UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

SUPERNUS PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. et al., Defendants.	Civil No. 13-4740 (RMB/JS) **OPINION** **(PUBLICLY FILED)**
SUPERNUS PHARMACEUTICALS INC., Plaintiff, v. ACTAVIS INC. et al., Defendants.	Civil No. 14-1981 (RMB/JS) **OPINION** **(PUBLICLY FILED)**

Appearances:

Charles M. Lizza
William C. Baton
Sarah A. Sullivan
Saul Ewing, LLP
One Riverfront Plaza
Newark, NJ 07102-5490

Edgar H. Haug
Sandra Kuzmich
Jason A. Lief
Nicholas F. Giove
Andrew S. Roper
Laura A. Chubb
Jonathan Herstoff

Rachel P. McClure
Kevin J. Georgek
Frommer Lawrence & Haug
745 Fifth Avenue, Floor 10
New York, NY 10051
Attorneys for Plaintiff

Charles A. Weiss
Howard S. Suh
Michael B. Eisenberg
Eric H. Yecies
Leisa Smith Lundy
Christopher M. Scott
Nicholas P. Chiara
Holland & Knight
31 West 52nd Street
New York, NY 10019

Liza M. Walsh
Jennifer Critchley
Eleonore Ofosu-Antwi
Christopher J. Borchert
Connell Foley LLP
One Newark Center
1085 Raymond Blvd, 19th Floor
Newark, NJ 07102
Attorneys for Defendants

BUMB, UNITED STATES DISTRICT JUDGE:

TABLE OF CONTENTS

I. INTRODUCTION 4
II. BACKGROUND 7
A. The Drug Approval Process 7
B. Epilepsy and the Anti-Epilepsy Drug Market 8
C. Supernus's Oxcarbazepine Drug Oxtellar XR® and the Patents-in-Suit 9
1. The Patents-in-Suit 9
2. Oxtellar XR® 12
D. Actavis's ANDA 13
III. LEGAL ANALYSIS 13
A. Claim Construction 16
1. Homogeneous Matrix 17
2. C_{min} and C_{max} 24
B. Infringement 25
1. The '898 and '131 Patents 26
2. The '600 Patent 80
C. Invalidity 88
1. Obviousness 90
2. Written Description 127
3. Indefiniteness 133
IV. CONCLUSION 135

I. INTRODUCTION

This is an action for patent infringement brought by Plaintiff Supernus Pharmaceuticals, Inc. ("Supernus" or "Plaintiff") against Defendants Actavis Inc., Watson Laboratories, Inc. - Florida n/k/a Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and ANDA, Inc. (collectively, "Actavis" or "Defendants") pursuant to 35 U.S.C. § 271(e)(2)(A) and §§ 271(a), (b), and (c).

This case involves Supernus's Oxtellar XR® product, a once-daily extended release oxcarbazepine tablet used to treat partial epilepsy seizures in adults and children above the age of six. Supernus seeks to prevent the Defendants from selling a generic version of Oxtellar XR®, in connection with Actavis's submission of Abbreviated New Drug Application ("ANDA") number 205444 seeking the approval of the U.S. Food & Drug Administration ("FDA") to market its generic ANDA product (the "Actavis Tablets") prior to the expiration of certain patents held by Supernus. Specifically, Supernus alleges that in selling its generic version of Oxtellar XR®, the Defendants will infringe U.S. Patent Nos. 7,722,898 (the "'898 Patent"), 7,910,131 (the "'131 Patent"), and 8,617,600 (the "'600 Patent") (collectively, the "Supernus Patents" or the "Patents-in-Suit").

Supernus is asserting claims 1, 6 to 8, 11, 18, and 19 of the '898 Patent, claims 6 to 8, 11, 18, 19, and 21 of the '131

Patent, and claims 1, 7 to 9, 12, 18, and 19 of the '600 Patent. The asserted claims all require a homogeneous matrix comprising the active pharmaceutical ingredient oxcarbazepine, a matrix forming polymer, a solubility enhancing agent, and a release promoting agent. Claim 1 of the '898 Patent provides:[1]

> 1. A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:
>
> (a) oxcarbazepine;
>
> (b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
>
> (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
>
> (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers.

[1] Although the '898, '131, and '600 Patents share the same specifications, they are slightly different. For convenience, citations to the specifications of the Patents-in-Suit are to the '898 Patent, unless otherwise noted.

The dependent claims of the '898, '131, and '600 patents generally specify the types of excipients for the matrix forming polymer, solubility enhancing agent, and release promoting agent. They also specify the ranges of fluctuation in pharmacokinetic parameters.

The Court conducted a seven-day bench trial from November 18, 2015 through December 4, 2015. It then permitted the parties to file post-trial briefing.[2]

After considering all the evidence, and for the reasons set forth below, the Court finds that: (1) the Defendants will infringe the '898 Patent and the '131 Patent; (2) the Defendants will not infringe the '600 Patent; and (3) all the Patents-in-Suit are valid. Accordingly, the Court enters judgment against Actavis and in favor of Supernus as to the '898 and '131 Patents and against Supernus and in favor of Actavis as to the '600 Patent. This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Rule 52(a).[3]

---

[2] The Court expresses its appreciation to counsel for their professionalism and valuable contributions to this litigation.

[3] The Defendants' oral motion made during trial for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) is GRANTED as to the '600 Patent only. Rule 52(c) permits such motions after "a party has been fully heard on an issue during a nonjury trial." During trial, the Court denied the motion as to the '898 and the '131 Patents, but exercised its discretion to reserve on the motion as to the '600 Patent. Tr. 879:4-8.

II. BACKGROUND[4]

A. The Drug Approval Process

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., the FDA must approve all new drugs before they may be distributed in interstate commerce. 21 U.S.C. § 355(a). To secure approval for a new drug, an applicant may file a New Drug Application ("NDA") that includes, inter alia, the number and expiration date of any patents which claim the drug or a method of using the drug if a claim of patent infringement could reasonably be asserted. Id. § 355(b)(2). "The FDA publishes the names of approved drugs and their associated patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations list, commonly referred to as the 'Orange Book.'" AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1045 (Fed. Cir. 2010). An applicant seeking approval to market a generic version of a drug that has already been approved may file an ANDA, which "allows an applicant to rely on the safety and efficacy information for the listed drug if the applicant can show that the generic drug is 'bioequivalent' to the listed drug." Id. (citing 21 U.S.C. §§ 355(b)(2), 355(j)).

[4] Because this civil action arises under the United States patent laws, Title 35 of the United States Code, this Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

"[F]or each patent listed in the Orange Book that claims either the listed drug or a use of the listed drug for which the applicant is requesting approval, an ANDA must include either one of four certifications or a 'section viii statement.'" AstraZeneca LP, 633 F.3d at 1046. If an applicant submits a certification, the applicant must certify "(I) that . . . patent information has not been filed, (II) that such patent has expired, (III) . . . the date on which such patent will expire, or (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug." 21 U.S.C. § 355(j)(2)(A)(vii)(I)—(IV). The last of these is known as a "paragraph IV certification." If an ANDA applicant submits a paragraph IV certification and a patent infringement suit is commenced within 45 days, then the FDA may not approve the ANDA application until the expiration of a 30-month statutory period. Id. § 355(c)(3)(C).

B. Epilepsy and the Anti-Epilepsy Drug Market

Epilepsy is a serious and chronic neurological disorder characterized by seizures. It cannot be cured, but it can be managed by anti-epileptic drugs ("AEDs"). Trial Transcript ("Tr.") 1195:20-1196:7 (Wheless Direct). Seizure control, through medication, is crucial and often challenging to achieve. Likewise, patients' compliance with their medication regimen is paramount given the potentially devastating consequences of a

patient not taking the medication properly. Id. at 1201:4-1202:15. Once a physician has established an effective AED regimen for a given patient, the physician will likely be reluctant to change the regimen for fear of breakthrough seizures or changes in the patient's tolerability for the medication. See, e.g., Tr. 1517:19-1519:1 (Rausser Direct); Tr. 1257:4-5 (Lado Direct).

Prior to the commercial release of Oxtellar XR®, there were over twenty different types of AEDs available on the market worldwide. Tr. 1242:24-1243:2 (Lado Direct). These included oxcarbazepine formulations, as well as medications with different active ingredients, such as carbamazepine. Some AEDs had already been reformulated for extended release. Id. at 1242:24-1243:6, 1244:24-1245:12. Oxcarbazepine, however, had not. Additionally, the available AEDs at the time utilized varying mechanisms or modes of action. Id. at 1243:8-15; DTX 471 at ACT-OXXR002757935. Twice daily oxcarbazepine first entered the market as branded Trileptal® in 2000. Several generic versions followed. Id. at 1241:17-1242:1.

C. Supernus's Oxcarbazepine Drug Oxtellar XR® and the Patents-in-Suit

1. The Patents-in-Suit

The Patents-in-Suit describe and claim a specific type of oxcarbazepine formulation for the treatment of seizures with a

"homogenous matrix" containing the active ingredient, oxcarbazepine, and excipients. The "homogeneous matrix" is central to the claimed invention.

a) The '898 Patent

On May 25, 2010, the United States Patent and Trademark Office (the "PTO") issued the '898 Patent, entitled "Modified-Release Preparations Containing Oxcarbazepine and Derivatives Thereof." PTX 1. The named inventors are Dr. Padmanabh P. Bhatt, Dr. Argaw Kidane, and Dr. Kevin Edwards. The '898 Patent was filed on April 13, 2007 as Application No. 11/734,874 and is related to Provisional Application No. 60/794,837, filed on April 26, 2006. The '898 Patent expires on April 13, 2027.

The '898 Patent covers an oxcarbazepine formulation administered once-daily for the treatment of seizures. Supernus asserts that before the '898 Patent, there were no once-daily oxcarbazepine tablets for the treatment of seizures. Tr. 56:4-60:13 (Bhatt Direct); PTX 1.17 at col. 1, ll. 20-col. 2, ll. 16. Although oxcarbazepine had been available for use twice daily in immediate-release form, there were no clinical studies showing that it would be effective once daily.

b) The '131 Patent

The '131 Patent, entitled "Method of Treating Seizures Using Modified Release Formulations of Oxcarbazepine," was filed on August 27, 2008 as Application No. 12/230,276, which was a

continuation of Application No. 11/734,874, filed on April 13, 2007. The '131 Patent is also related to Provisional Application No. 60/794,837, filed on April 26, 2006. The '131 Patent was issued by the PTO on March 22, 2011 and expires on April 13, 2027. The '131 Patent covers a method of treating seizures by administering an oxcarbazepine pharmaceutical formulation.

c) The '600 Patent

The '600 Patent, entitled "Modified Release Preparations Containing Oxcarbazepine and Derivatives Thereof," was filed on May 21, 2012 as Application No. 13/476,337, which was a continuation of Application No. 13/137,382, filed on August 10, 2011, which was in turn a continuation of Application No. 12/230,275, filed on August 27, 2008, which is a continuation of Application No. 11/734,874, filed on April 13, 2007. The '600 Patent is also related to Provisional Application No. 60/784,837, filed on April 26, 2006. The '600 Patent was issued by the PTO on December 31, 2013 and it expires on April 13, 2027. The '600 Patent also covers an oxcarbazepine formulation for the treatment of seizures. Its terms are largely similar to those of the '898 Patent but also include certain percentages by weight of the formulation and ***in vitro*** dissolution limitations.

The Defendants dispute Supernus's claims relating to the each of the Patents-in-Suit on grounds of non-infringement and invalidity.

2. Oxtellar XR®

In October 2012, the FDA approved NDA No. 202810 for an oxcarbazepine extended-release oral tablet, which Supernus markets under the name Oxtellar XR®. Its sole active ingredient is oxcarbazepine, an anti-epileptic drug that has been known for almost 50 years. Oxtellar XR® is indicated for the treatment of seizures in adults and children above six years of age. Stipulated Facts ("SF") [Docket No. 353] p. 6 ¶ 1; PTX 388.1. Oxtellar XR® contains oxcarbazepine in an extended release formulation that is intended to be taken less frequently than immediate-release oxcarbazepine. SF p. 6 ¶ 3.

The Patents-in-Suit cover the once-a-day oxcarbazepine formulation embodied by Oxtellar XR® and the use of this formulation. Tr. 1635:5-1641:17 (Little Direct); Tr. 1690:17-1692:13 (Thakker Direct); Tr. 355:6-357:13 (Bugay Direct); PTX 388.

Supernus launched Oxtellar XR® on February 1, 2013. SF p. 13 ¶ 34. At the time of its release, and to this day, Oxtellar XR® is the only FDA-approved oxcarbazepine formulation for once-a-day administration for the treatment of seizures. SF p. 6 ¶ 3, p. 13 ¶ 35. Prior to the commercial release of Oxtellar XR®,

oxcarbazepine was available only in immediate release, twice daily formulations. Trileptal®, the brand name twice daily oxcarbazepine formulation, was released in 2000 and generic versions followed. As a once daily oxcarbazepine formulation, Oxtellar XR® overcame certain difficulties presented by the immediate release, twice daily medications available at the time, including concerns regarding patient compliance, fluctuations in blood plasma concentration, and disruptive side effects.

D. Actavis's ANDA

On March 20, 2013, less than two months after the commercial launch of Oxtellar XR®, Actavis filed ANDA No. 205444 with the FDA seeking regulatory approval to market extended-release oxcarbazepine oral tablets in 150 mg, 300 mg, and 600 mg dosages. Actavis's ANDA identifies the listed drug product that is the basis for the submission as Oxtellar XR®. Actavis's ANDA included a paragraph IV certification asserting that the '898, '131, '600 Patents are invalid, unenforceable, or will not be infringed by the manufacture or sale of its generic extended-release oxcarbazepine tablets. Actavis's ANDA is currently pending.

III. LEGAL ANALYSIS

To prove infringement, the patentee must show that it is more likely than not that the proposed ANDA product would, if

commercially marketed, meet all of the claim limitations of the Patents-in-Suit. See Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1287 (Fed. Cir. 2010) (en banc); Abbot Labs. v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002) (infringement analysis turns on whether accused product satisfies every limitation of the claim in question). In other words, the patentee "has the burden of proving infringement by a preponderance of the evidence." Kegel Co., Inc. v. AMF Bowling, Inc., 127 F.3d 1420, 1425 (Fed. Cir. 1997); SmithKline Diagnostics, Inc. v. Helena Labs. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988). Determining whether an accused product infringes the patent involves a two-step analysis. Kegel, 127 F.3d at 1425. The Court must first construe the scope and meaning of the asserted patent claims and then compare the accused product to the properly construed claims. Id.

Before beginning this two-step analysis, the Court observes that, although the parties do not agree on the definition of a person of ordinary skill in the art, sometimes referred to as a POSA, compare Joint Final Pre-Trial Order [Docket No. 353], p. 41 ¶ 152, with id. at p. 99 ¶ 173,[5] they have made no arguments

[5] Supernus proposes the following definition of a person of ordinary skill in the art:

> a person in the 2006 time frame with at least a Bachelor of Science Degree in Pharmaceutical Sciences or a related field and approximately 3-5 years of experience in the

as to which definition the Court should adopt. Furthermore, the parties have not identified how the Court's analysis would differ depending on the definition adopted. Nonetheless, the Court sees no material difference between the definitions put forth by the parties and finds that its claim construction, infringement, and validity analyses would be the same under either definition.

> field of drug delivery technology or a related field (or a person of commensurate education and experience).

Joint Final Pre-Trial Order, p. 41 ¶ 152.

Actavis, in turn, proposes the following definition of a person of ordinary skill in the art:

> The person of ordinary skill in the art is engaged in the design and development of extended-release dosage forms. The person of ordinary skill in the art has at least a B.S. degree in the biological, chemical, or pharmaceutical sciences, or materials science or chemical engineering, and several years of experience in the field of pharmaceutical formulation development, with the amount of post-graduate experience depending upon the level of formal education obtained. Further, the person of ordinary skill in the art may possess the knowledge of a collaborative team of ordinarily skilled artisans in related disciplines of pharmaceutical sciences that would work together in the relevant field. The person of ordinary skill in the art would either have his or her own education and experience in the fields of pharmaceutics and pharmacodynamics or be part of a team that includes a skilled artisan in the fields of pharmacokinetics and pharmacodynamics. Therefore, for the elements in the patent claims that address pharmacokinetics and/or treatment-related limitations, the skilled formulator would have ready access to and the ability to communicate with one of ordinary skill in the art of pharmacokinetics and pharmacodynamics.

Id. at p. 99 ¶ 173.

A. Claim Construction

As for the first step, on August 14, 2014, the parties filed their Joint Claim Construction and Prehearing Statement pursuant to Local Patent Rule 4.3 and the Court's June 4, 2014 Scheduling Order [Docket No. 138]. On December 9, 2014, the Court conducted a Markman hearing [Docket No. 177]. Although the parties disputed the construction of several claim terms, the Court found that most terms required no construction. There were, however, two terms that required construction: "homogeneous matrix" and "C_{min} and C_{max}."[6]

Claim construction is a question of law. See Markman v. Westview Instruments, Inc., 517 U.S. 370, 391 (1996). The Court determines the meaning of disputed claim terms as understood by one of ordinary skill in the art at the time of invention. See Phillips v. AWH Corp., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Claim terms generally should be given their ordinary and customary meaning to a person of skill in the art at the time of the invention. See id. To determine the ordinary meaning, the Court first looks to the intrinsic evidence, which includes the claims, the specification and the prosecution history. Id. at 1312–17 ("Like the specification, the

[6] The Court also construed "once-a-day administration" to mean "administered once per day every 24 hours."

prosecution history provides evidence of how the PTO and the inventor understood the patent.").

The starting point for claim interpretation is the claim language itself, which can "provide substantial guidance as to the meaning of particular claim terms." Id. at 1314. Thus, the language of the claims is paramount. Pass & Seymour, Inc. v. Int'l Trade Comm'n, 617 F.3d 1319, 1324 (Fed. Cir. 2010); see Chef Am., Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1374 (Fed. Cir. 2004) ("in accord with our settled practice we construe the claim as written, not as the patentees wish they had written it"). The claims, however, "must be read in view of the specification, of which they are a part." Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir.), aff'd, 517 U.S. 370 (1996). Extrinsic evidence, such as dictionaries, may be consulted to assist in understanding disputed terms. Phillips, 415 F.3d at 1318. Extrinsic evidence, however, must be "considered in the context of the intrinsic evidence." Id. at 1317-19.

1. Homogeneous Matrix

The Court construed the term "homogeneous matrix" as "a matrix in which the ingredients or constituents are uniformly dispersed." The parties had proposed the following construction:

Claim Term	Supernus's Construction	Actavis's Construction
"homogeneous matrix"	"a substantially uniform dispersion of one or more constituents in a given volume" [alternate construction] "matrix in which the constituents are homogeneously dispersed"	"matrix in which the ingredients have a uniform distribution"

Supernus initially argued that a person skilled in the art would understand that the adjective "homogeneous" required substantial uniformity of the matrix constituents rather than complete uniformity on a molecular level. By requiring a "substantially uniform dispersion," Supernus argued, the claim language avoids requiring an unachievable absolute condition. In post-Markman briefing, and upon an unrebutted record that complete uniformity on a molecular level was not possible (or even desired)[7], Supernus provided an alternate construction:

[7] Dr. Steven Little's testimony that a person skilled in the art would understand that complete molecular uniformity is not possible or even desired in pharmaceutical formulations was essentially unrebutted. See Markman Tr. 73:14-74:8 [Docket No. 179]:

> Q. Professor, why are you focusing on this distinction of complete or molecular uniformity?
>
> A. Well, I can imagine processes where you could achieve molecular uniformity, complete uniformity where everything is dissolved and then crystalized, or something together where you would get like perfect arrangement or order, but that's -- you know, we don't use those kind [sic] of processes to make especially solid oral dosage forms here. The types of processes

"matrix in which the constituents are homogeneously dispersed." Pl. Supp. Claim Construction Br. at 4 [Docket No. 192].

Supernus's initial proposed construction is problematic. First, it adds language to the claim — the word "substantially" — that does not appear in the claim and has no support in the intrinsic evidence. Second, it reads the "matrix" limitation out of the claim. That is, under Supernus's initially proposed construction, there is no requirement that the element be in the form of a matrix. There is no need to write out the term "matrix," however, as there is no genuine dispute among the parties that the term excludes the coating or outer core. Indeed, Defendants' own proposal is a "matrix in which" the ingredients are dispersed.

> that are used in the patents-in-suit and common in the field are, like I said, they are mechanical agitation, it's -- it's in one way kind of similar to what you'd see with a kitchen mixer, you know, where you are adding sugar and a whole bunch of things together to make cookies. You know, you get things that end up sticking together because of the egg, which is kind of like the binder. But you end up getting two sugar particles sticking to each other. It's just sort of the way it works. It doesn't disperse out perfectly like that.
>
> So I just felt it was important to help the Court to understand that you can't get that kind of uniformity using these processes that are very standard, nor do you really need to get that kind of uniformity. As long as it's substantially uniform it functions just fine.

The prosecution history elucidates why the term "homogeneous" was added to the claim to exclude the coating: to clarify that, unlike the prior art identified by the Patent Examiner, the claimed formulation was contained in a homogeneous matrix. The Patent Examiner broadly construed the term "matrix" to include the coating of the tablet. PTX 5.281. Supernus took issue with such a broad construction, arguing that a person of ordinary skill in the art would not understand the term matrix to include the coating but rather a pharmaceutical composition wherein the components were "***contained in the matrix***." PTX 5.267 (emphasis in original). The Patent Examiner disagreed, writing that "the term 'a matrix comprising' in amended Claim 1 is not limited to a homogeneously admixed mixture of the four components, as inferred by Applicant's reply." PTX 5.281. Because the claim did not limit it as such, the Examiner rejected it. What followed was Supernus's proposal to amend the claim "to include language which specifies that the components of the pharmaceutical formulation are in a homogeneous admixture." PTX 5.289 (emphasis added). This amendment was viewed by the Examiner as "promising" to overcome the rejection. Id. Supernus thereafter amended the claim to a pharmaceutical

formulation comprising a "homogeneous matrix," which the Examiner allowed.[8] PTX 5.298; PTX 5.406.

Moreover, "substantially" is unnecessary because, as both parties acknowledge, the ordinary meaning of homogeneous is "loosely . . . used to describe a mixture or solution composed of two or more compounds or elements that are uniformly dispersed in each other." Hawley's Condensed Chemical Dictionary 655 (15th ed. 2007) [Docket No. 152-2] (emphasis added). As Hawley's Condensed Chemical Dictionary, cited by both parties, states:

> Actually, no solution or mixture can be homogeneous; the situation is more accurately described by the phrase "uniformly dispersed." Thus so-called homogenized milk is not truly homogeneous; it is a mixture in which the fat particles have been mechanically reduced to a size that permits uniform dispersion and consequent stability.

Hawley's Condensed Chemical Dictionary 577 (14th ed. 2001) [Docket No. 153-5] (emphasis added). See also Webster's II New College Dictionary 542 (3rd ed. 2005) [Docket No. 153-6] ("uniform throughout in structure or makeup"); Grant & Hackh's Chemical Dictionary 286 (5th ed. 1987) [Docket No. 152-2] ("Of uniform or similar nature throughout"); Mosby's Dictionary of

[8] Whether Supernus's amendment to Claim 1 to say "homogeneous matrix" as opposed to "homogeneous admixture" as it had proposed to the Examiner was a malapropism or intended is unclear. See Declaration of Steven R. Little, Ph.D. at p. 23-26 [Docket No. 153-10]. Regardless, the Examiner allowed the claim as amended.

Medicine, Nursing & Health Professions 899 (7th ed. 2006) [Docket No. 152-2] ("having a uniform quality throughout").

The specifications of the Patents-in-Suit support a construction that uses the ordinary term of homogeneous without the qualifier, substantially. Dr. Little explained the high shear granulation manufacturing method disclosed by the Patents-in-Suit in Example 4: the ingredients are added to a high shear granulator; the ingredients are blended by running the blade for three minutes and water is then sprayed onto the "mixing blend," the wet granules are dried in an oven; the dry granules are screened through an 18-mesh screen; the granules are then blended with a lubricant; and tablets are then formed on a rotary tablet press. Tr. 614:14-22 (Little Direct); '898 Patent, col. 10, ll. 37-55; see also id. at col. 5, ll. 5-8 ("The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.").

Indeed, Dr. Little appeared to recognize that adding the word "substantially" was not needed.

> THE COURT: But it seems as if you've been saying that it is understood to a person skilled in the art that this perfect uniformity is never achieved. And so, therefore, it seems to me adding the word "substantially" is really not needed because everyone understands exactly what it is that you are saying, that you don't get this perfect uniformity ever; it's impossible.

THE WITNESS: Right. So this is a really good question. Because when I talk to students, for instance, and they are looking at something, you could look at it with your eye and you could think that it's uniform. Right? But then you zoom in a little bit. And I telling [sic] them, you know, look at it with some microscopy and take a look and see what you think. And then they see that. You know, you could see even a distribution of sizes of heterogeneities in the system. So I think it's technically true that a person of ordinary skill would understand that that would be the case. But if you look at the wrong size scale or something like that, you could say oh, look, this is not homogeneous.

THE COURT: But you understand that the test that I use is a person skilled in the art.

THE WITNESS: Hmm.

. . .

THE COURT: Okay. And so it seems to me that in reading the patent, as long as the matrix includes the four things that we've been talking about, the oxcarb, the polymer, the matrix forming polymer, the agent that enhances the solubility and the release promoting agent, as long as those four things are uniformly dispersed in the matrix, that's the matrix.

THE WITNESS: Um-hum.

THE COURT: So you have, you know, one of one, one of two, one of three, one of four. That's uniformity. You are never going to get it perfect, but -- everyone understands you never are going to get it perfect.

THE WITNESS: Um-hum.

THE COURT: And so a person skilled in the art doesn't need to be told "substantially."

THE WITNESS: I think - -

THE COURT: Do you agree with that?

THE WITNESS: Yes.

Markman Tr. 125:10-127:1.

Thus, a "homogeneous matrix" means "a matrix in which the ingredients or constituents are uniformly dispersed."

2. C_{min} and C_{max}

The Court construed C_{min} to mean "minimum concentration in blood or plasma at steady state." The Court construed C_{max} to mean "maximum concentration in blood or plasma at steady state."

The parties had proposed the following constructions:

Claim Term	Supernus's Construction	Actavis's Construction
"C_{min}"	"minimum concentration in blood or plasma at steady-state"	"minimum concentration in blood once steady state is achieved"
"C_{max}"	"maximum concentration in blood or plasma at steady-state"	"maximum concentration in blood"

First, the parties propose nearly identical constructions for C_{min} except that the Defendants' definition refers only to blood rather than blood or plasma. However, the Patents-in-Suit use the words interchangeably. '898 Patent, col. 5, ll. 38-41 ("These types of release profiles ensure that the C_{max} (maximum concentration of the drug in blood/plasma) is kept within the therapeutic window while extending the maintenance of an effective drug level in the body"); '600 Patent, col. 5, ll. 43-47, '131 Patent, col. 5, ll. 42-45. As a further example,

Example 7 explains that the oxcarbazepine and monohydroxy derivative ("MHD") data shown in Figures 12 and 13 was obtained by analyzing "blood samples," '898 Patent, col. 12, ll. 33-37; '131 Patent, col. 12, 11. 32-36; '600 Patent, col. 12, ll. 34-38 (emphasis added), while the Y-axes of Figures 12 and 13 are labeled as "Plasma MHD conc. (µg/ml)" and "Plasma OXC conc. (µg/ml)," respectively. '898 Patent, Figs. 12, 13 (emphasis added); '131 Patent, Figs. 12, 13; '600 Patent, Figs. 12, 13; see also Declaration of Dhiren R. Thakker, Ph.D. at ¶ 64 [Docket No. 153-11]. (explaining how the specifications (e.g., Example 7) use the words interchangeably).

As to the remaining dispute, it is clear that C_{max} must be measured under steady state conditions. Actavis's proposed construction does not specify the condition under which C_{min} and C_{max} are to be measured. Moreover, it is clear from the Patents-in-Suit that C_{max} must also be evaluated at steady-state, like C_{min}, for which the Defendants agree. To hold otherwise and adopt the Defendants' proposed construction could lead to the absurd result of C_{max} being less than C_{min}. Accordingly, C_{min} and C_{max} are the minimum and maximum concentration, respectively, in blood or plasma at steady-state.

B. Infringement

As for the second step of the infringement analysis, the Court must determine whether the accused product contains every

limitation of the properly construed claims. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1467 (Fed. Cir. 1998).

1. The '898 and '131 Patents

The '898 and '131 Patents are directed to "controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration." '898 Patent, col. 1, ll. 14-16; '131 Patent, col. 1, ll. 16-18.

Supernus asserts that the Defendants will infringe claims 1, 6 to 8, 11, 18, and 19 of the '898 Patent and claims 6 to 8, 11, 18, 19, and 21 of the '131 Patent. Claim 1 of each of the Patents, the only independent claim, requires a "pharmaceutical formulation comprising a homogeneous matrix," which in turns comprises four constituents:

> (a) oxcarbazepine;
>
> (b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
>
> (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
>
> (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-

> maleic mono-ester copolymer, and Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers. The dependent claims of the '898, '131, and '600 patents generally specify the types of excipients for the matrix forming polymer, solubility enhancing agent, and release promoting agent, and also specify the ranges of fluctuation in pharmacokinetic parameters.

Claim 1 of the '898 Patent additionally requires that the pharmaceutical formulation be "for once-a-day administration." Claim 1 of the '131 Patent discloses a "method of treating seizures" through the administration of the pharmaceutical formulation described above.[9] The remaining asserted claims are all directly or indirectly dependent on Claim 1, meaning that they include all of the limitations of Claim 1 as well as additional limitations.

a) Oxtellar XR®

Supernus's Oxtellar XR® is presently the only commercial embodiment of the Patents-in-Suit available on the market. The parties do not dispute, and the expert testimony at trial confirms, that Oxtellar XR® comprises a homogeneous matrix of the four recited elements. See, e.g., Tr. 960:11-964:1 (Muzzio Cross); Defendants' Proposed Findings of Fact ("DFOF") ¶ 21 [Docket No. 392].

[9] Although Supernus does not assert Claim 1 of the '131 Patent, the asserted claims of the '131 Patent all depend directly or indirectly on Claim 1, and so it must be addressed.

Additionally, Dr. Kidane, one of the inventors on the Patents-in-Suit, testified by video deposition that his understanding of what constitutes a "homogeneous matrix" is that "the components are mixed together." Tr. 463:20-22 (Kidane Depo).[10] He went on to testify that the mixing that takes place during the manufacturing process of the Oxtellar XR® tablets creates homogeneity. Id. at 464:16-465:25. Dr. Little likewise agreed that, when one follows the manufacturing process as set forth in the examples in the Patents-in-Suit, as Supernus does to formulate Oxtellar XR® tablets, a homogeneous matrix is necessarily achieved. Tr. 613:18-614:13 (Little Direct). Dr. Kidane also explained that Supernus conducts uniformity testing on the Oxtellar XR® product to confirm the homogeneity of the

[10] The Court denied the Defendants' application to strike the deposition testimony of Vitaliy Disman and Argaw Kidane and to direct the live testimony of both witnesses [Docket No. 365]. There is no dispute that Mr. Disman and Dr. Kidane work and live in Maryland, more than 100 miles from the Camden federal courthouse. The Court agrees with Supernus that, under Federal Rule of Civil Procedure 45(c), it cannot mandate the live testimony of these witnesses as they live and work in a different state and over 100 miles from the courthouse. Furthermore, their deposition testimony is admissible under Rule 32(a)(4), which provides that "[a] party may use for any purpose the deposition of a witness, whether or not a party, if the court finds: . . . that the witness is more than 100 miles from the place of hearing or trial . . . unless it appears that the witnesses's absence was procured by the party offering the deposition." In any event, it is hard to see how Actavis suffered any unfair prejudice by the introduction of this deposition testimony at trial. Actavis noticed and took the depositions and had ample opportunity to examine the witnesses.

tablet matrix. Specifically, he testified that the uniformity testing performed by Supernus "show[s] that the matrix of the product that we have is -- has that homogeneous matrix." Tr. 461:14-17 (Kidane Depo).

Similarly, it is undisputed that Oxtellar XR® contains oxcarbazepine. SF p. 6 ¶ 3. Likewise, Oxtellar XR® contains several matrix-forming polymers as described in element 1(b) of Claim 1 in the form of silicified microcrystalline cellulose ("SMCC"), hypromellose (also known as HPMC), and Kollidon 25 (a form of povidone, also known as polyvinyl pyrrolidone or PVP). Tr. 1636:8-12 (Little Direct); PTX 325.1. It also contains agents that enhance the solubility of oxcarbazepine, as described in element 1(c), in the form of sodium lauryl sulfate ("SLS"), hypromellose, and povidones. Tr. 1626:16-22 (Little Direct); PTX 325.1. Finally, Oxtellar XR® contains Eudragit L 100-55, which the parties do not dispute is a release promoting agent. Tr. 1637:9-15 (Little Direct); PTX 325.1.

b) The Actavis ANDA Product

The parties have stipulated that the Actavis Tablets have the following composition:

Composition of Oxcarbazepine Extended-release Tablets, 150 mg, 300 mg and 600 mg

SF pp. 12-13 ¶ 33; PTX 116.6.

Supernus contends that the Actavis Tablets infringe Claim 1 of the '898 Patent and several claims of the '131 Patent that depend upon Claim 1 of the '131 Patent. Actavis concedes that its product contains certain elements of Claim 1, but not all. Specifically, Actavis concedes that its tablets are meant for once-a-day administration for the treatment of seizures. SF p. 11 ¶ 21; PTX 98.4. There is no dispute that Actavis's label and prescribing information state that the Actavis Tablets are to be used to treat seizures. PTX 98.4; Tr. 597:18-598:9 (Requests for Admission).

Actavis further concedes that its tablets contain element 1(a) oxcarbazepine, element 1(b) matrix-forming polymers in the form of [redacted], and at least one element 1(d) release promoting agent comprising a polymer with pH-dependent solubility in the form of [redacted].[11] SF p. 13 ¶¶ 36-39; PTX 116.6. Actavis, however, disputes the presence of a homogeneous matrix and an agent that enhances the solubility of oxcarbazepine. The Court's infringement analysis shall, therefore, focus on these two elements.

c) Claim 1

(1) Homogeneous Matrix

All of the asserted claims require a pharmaceutical formulation of oxcarbazepine "comprising a homogeneous matrix . . . ." '898 Patent, Claim 1; '131 Patent, Claim 1; '600 Patent, Claim 1. As noted above, the Court construed "homogeneous matrix" to mean a "matrix in which the ingredients or constituents are uniformly dispersed." Docket No. 244. Further, as mentioned, the phrase "homogeneous matrix" was added

[11] The parties dispute whether [redacted], an ingredient found in the Actavis Tablets, satisfies element 1(d). This is not relevant for the infringement analysis regarding the '898 and '131 Patents for reasons discussed herein. It is, however, relevant to the infringement analysis regarding the '600 Patent and will be addressed infra.

to Claim 1 through two consecutive Office Action responses to overcome prior art references that purportedly disclosed element 1(d) release promoting agents in the coating. See PTX 5.205-07, 262-70, 290-300. The term "homogeneous matrix" was added to the claims to distinguish Supernus's invention, which has all four matrix components in the tablet core, from the prior art references containing certain matrix constituents solely in the coating (which the Patent Examiner had viewed to be part of the matrix). The term was not added to describe the degree of uniformity or homogeneity of the Supernus invention. PTX 5.262-70, 295, 298-99.

To carry its burden of proving infringement as to the "homogeneous matrix" limitation, Supernus presented evidence regarding the manufacturing process by which Actavis creates its ANDA product, FDA-required uniformity testing, and chemical imaging. The Court will address each in turn.

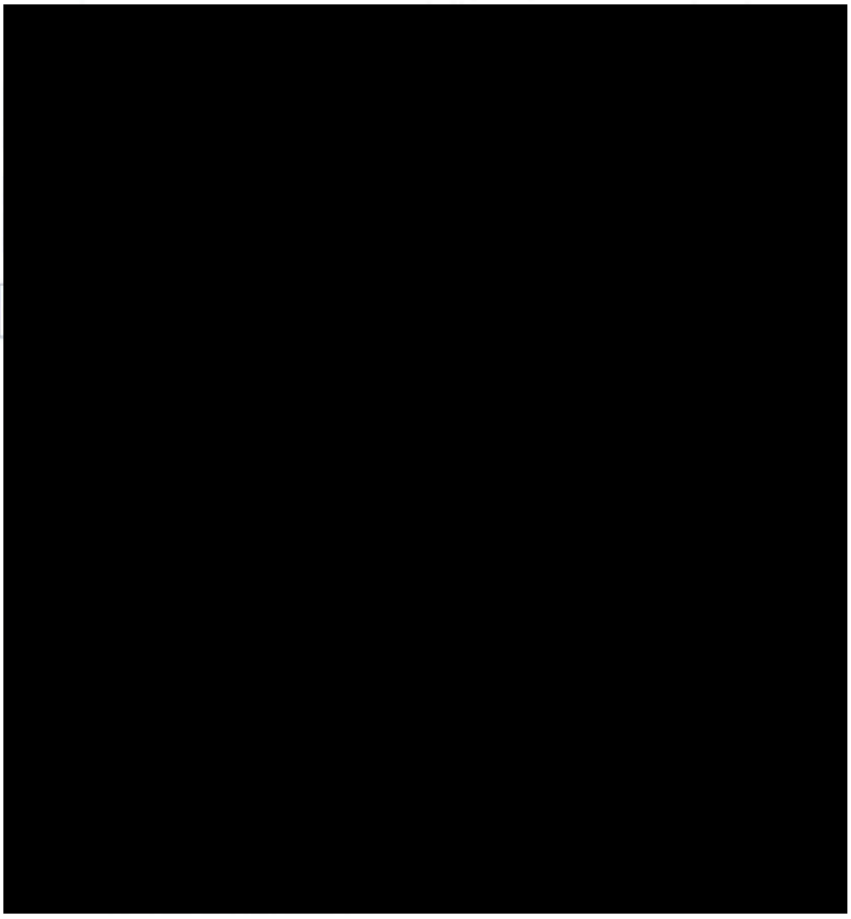
Manufacturing Process

The Plaintiff contends that Actavis's manufacturing process proves that its tablets comprise a homogeneous matrix in which the constituents are uniformly dispersed. To support this position, Supernus presented the testimony of several expert witnesses.

As a starting point, the parties, through their experts, agree that "absent a specific objective not to be homogeneous,

the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation that would comprise a uniform dispersion of ingredients[.]" Tr. 1493:12-19 (Hopfenberg Cross); see also Tr. 341:20-23 (Bugay Direct); Tr. 361:13-18 (Bugay Cross). No evidence has been presented that indicates that the Actavis formulators sought to stray from this default objective. In fact, Actavis's manufacturing process establishes that its tablets comprise a homogeneous matrix.

Actavis's manufacturing process involves several steps. The manufacturing as set forth in Actavis's Quality Overall Summary, included in its ANDA, is as follows:



PTX 50.51

Dr. Little also testified at length regarding Actavis's manufacturing process. The first step, [redacted] Tr. 619:23-620:9 (Little Direct). In its Product Development Report, Actavis claims that [redacted] PTX 42.55.

The second step, [redacted] Tr. 620:10-17. The purpose of [redacted] Id. at 620:15-17; PTX 50.57. In the third step, [redacted] PTX 42.55; Tr. 620:18-621:4 (Little Direct).

The fourth step, [redacted] Tr. 621:5-14 (Little Direct). Actavis discloses in its ANDA that this [redacted]

[redacted] PTX 42.75.

Dr. Fernando Muzzio, Actavis's expert in chemical imaging, countered that Actavis's manufacturing process results in a non-homogeneous matrix because of [redacted], which is, according to him, "universally used by formulators everywhere to promote uniform homogeneous granulation." Tr. 929:17-23 (Muzzio Direct). He also stated that Actavis's granulation process results in "relatively large granules . . . And because the granules are relatively large, they could not appear everywhere in the tablet in the same proportion." Id. at 929:23-930:9. In Dr. Muzzio's opinion, this results in a non-homogeneous matrix in the Actavis Tablets. When asked by the Court whether homogeneity is simply a product of the type of blender used, Dr. Muzzio responded that "[t]hat's close to one of the concepts I'm using." Tr. 967:5-11 (Muzzio Cross). Actavis's granulation process [redacted] as compared to Supernus's process, which, according to Dr. Muzzio, results in a lower "level of intermingling of ingredients . . . [and] granules that are more diverse." Id. at 967:12-19.

Given Actavis's own description of the purpose of each step in its manufacturing process, the Court gives these opinions little weight. See, e.g., PTX 42.55 ([redacted]); PTX 42.75 ([redacted]

[redacted]).

Furthermore, the Patents-in-Suit clearly contemplated the formation of granules and did not view the fact that certain ingredients were added after the formation of granules to be an impediment to the creation of a homogeneous matrix. See, e.g., '898 Patent, col. 5, ll. 1-9; col. 5, l. 22; Tr. 956:7-958:5 (Muzzio Cross).

The final step [redacted] Dr. Little persuasively testified that the homogeneity achieved in the blend by the previous steps is carried over to the compressed tablet. Tr. 621:25-622:3 (Little Direct). In fact, in Dr. Little's expert opinion, the manufacturing process followed by Actavis in formulating its ANDA tablets results in a homogeneous matrix in those tablets. Id.

Dr. David Bugay, Supernus's expert who is a physical analytical chemist who specializes in spectroscopy, too reviewed Actavis's manufacturing process as set forth in its ANDA. The manufacturing process confirmed his conclusion that the constituents are uniformly dispersed in the Actavis Tablets such that the tablet comprises a homogeneous matrix. Tr. 351:12-20 (Bugay Direct).[12] What's more, the inventors of the Patents-in-

[12] Even Dr. Irwin Jacobs, Actavis's former expert that it has since abandoned, characterized the Actavis ANDA product as "a

Suit stated during prosecution history that "[o]ne of ordinary skill in the art would appreciate that the formulations derived according to the [manufacturing] protocol set forth in the Examples would necessarily comprise a homogeneous matrix." PTX 5.298. Example 4 in the '898 Patent sets forth a manufacturing process that involves blending and high shear granulation prior to tableting. '898 Patent, col. 10, ll. 35-56. [redacted] See PTX 42.41; Tr. 614:14-22 (Little Direct).

The Court finds that Actavis's manufacturing process results in a homogeneous matrix in its tablets.

FDA Uniformity Testing

Pursuant to FDA regulation, all pharmaceutical formulations must pass a series of uniformity tests, including blend uniformity, content uniformity, and dissolution testing, prior to being approved. These tests, which the Actavis Tablets have indisputably passed, likewise demonstrate that the Actavis Tablets comprise a homogeneous matrix in which its constituents are uniformly dispersed.

---

homogeneous matrix" after reviewing Actavis's manufacturing process. Tr. 429:11-24 (Jacobs Depo). The parties dispute the admissibility of Dr. Jacobs's testimony at trial. The Court does not rely on any testimony of Dr. Jacobs in reaching its conclusions and, therefore, need not reach the issue of its admissibility.

The FDA requires that blend uniformity testing be performed on all pharmaceutical formulations to ensure the adequacy of mixing. Prior to receiving FDA approval, all pharmaceutical formulations must pass blend uniformity testing. Blend uniformity testing assesses the uniformity of all blended ingredients prior to tableting. It tests "the adequacy of the mixing" by testing various samples from the blend to "determine whether or not [the] product is uniformly dispersed." Tr. 627:5-13 (Little Direct).

Dr. Jack Chen, Actavis's director of analytical chemistry and its 30(b)(6) witness on homogeneity testing, explained the underlying purpose of the uniformity tests mandated by the FDA:

> Q. What is the purpose of running [blend uniformity testing]?
>
> A. It's required by regulation.
>
> Q. Okay. But what is the purpose underlying the regulation?
>
> A. To see how your blend, whether it's homogeneous or not.
>
> Q. Okay. And a positive result or an in-specification result for blend uniformity would indicate that your product is homogeneous?
>
> A. Correct.

Tr. 794:8-13 (Chen Depo) (emphasis added).

Dr. Little also testified that blend uniformity testing tests whether the constituents of the product are "uniformly

dispersed." Tr. 627:5-21 (Little Direct). He further explained that "there's an understanding that if this is blended properly . . . that what you would have is you would have a uniform final product." Id.

Dr. Muzzio testified that the homogeneity of the blend is irrelevant to the term "homogeneous matrix" as construed by the Court because the blend is not a matrix and because blend uniformity testing does not address the spatial distribution of ingredients within the final tablet. Tr. 936:20-937:1 (Muzzio Direct). These arguments miss the point. Although blend uniformity tests examine only the blend, not the final tablet, the Court is persuaded by Dr. Little's expert opinion that if the constituents are properly blended, the final product will necessarily be uniform. Tr. 627:14-21 (Little Direct).

This is likewise true even though blend uniformity testing only directly measures the active ingredient in the blend, here, oxcarbazepine. Once the uniformity of the active ingredient is established, a person of skill in the art would assume that all the other constituents of the blend are also uniformly dispersed. Tr. 630:16-631:4 (Little Direct); Tr. 729:21-731:1 (Little Redirect).[13] The uniformity of the active ingredient is

[13] Dr. Muzzio, Actavis's expert, agreed that a person of ordinary skill in the art generally assumes the uniform dispersion of the excipients once it has been established that the active ingredient is uniformly dispersed. He, however, takes issue

necessarily impacted by the uniformity of the excipients. In Dr. Little's opinion, excipients that are not uniformly dispersed would result in a non-uniform distribution of the active ingredient. Id. at 730:7-731:1.

It is undisputed that the Actavis ANDA product passed blend uniformity testing. PTX 170.3; PTX 572.3. Dr. Little reviewed the results of blend uniformity testing as found in the Actavis ANDA and concluded that the Actavis Tablets are uniform. Tr. 630:2-14 (Little Direct).

In addition to blend uniformity testing, the FDA also requires content uniformity testing. Content uniformity testing, also known as unit dose uniformity testing, is conducted after the blend has been compressed into tablets. This test measures the active ingredient in the final tablet in order to ensure that the same amount of the active ingredient is present across tablets. Tr. 631:11-632:14 (Little Direct). Dr. Little explained that in measuring the active ingredient in each tablet, content uniformity testing also necessarily measures the quality of mixing in, as well as the homogeneity and uniformity

---

with this assumption. See Tr. 1057:22-1059:19 (Muzzio Cross). Whether or not Dr. Muzzio's concerns are valid, they do not change the fact that this is the methodology widely used by those skilled in the art. The Court must use the perspective of a person of ordinary skill in the art.

of the final tablet. Id. at 632:1-9.[14] As with blend uniformity testing, the uniform dispersion of the excipients is assumed once the uniformity of the active ingredient is established. Id. Dr. Little cogently explained that if the excipients were not uniformly dispersed, there would be localization of all constituents, including the active ingredient. Id. An in-specification result for content uniformity testing establishes that there is no localization of the active ingredient and, therefore, also no localization of the excipients.

The Actavis Tablets passed content uniformity testing. PTX 50.62; PTX 116.27. The results of the content uniformity testing are consistent with Actavis's manufacturing process and confirm that the Actavis Tablets comprise a homogeneous matrix. Tr. 634:14-635:3 (Little Direct).

Actavis additionally performed ***in vitro*** dissolution tests on its tablets for submission to the FDA. Actavis tested twelve tablets from each strength of its tablets. PTX 39.8, 20, 32; Tr. 635:22-637:16 (Little Direct). Supernus contends that the

[14] Dr. Muzzio, Actavis's expert, actually agrees. Just last year, in an article entitled The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Blends, Dr. Muzzio explained that "In-process dosage unit analysis . . . is an accurate and reflective measure of homogeneity of the product. . . . It accounts for potential segregation after blending. . . . In general, content uniformity of the final dosage form is dependent on the homogeneity of the powder mixture in the blender." Tr. 1049:17-1051:6 (Muzzio Cross).

results of the dissolution tests likewise confirm that the Actavis Tablets comprise a homogeneous matrix. The Court agrees.

Dr. Little explained that dissolution testing "measure[es] how the dosage unit performs. So if the dosage unit is uniformly dispersed, what will happen is, is that the dosage form will behave the same from tablet to tablet to tablet. So you're measuring [the] release profile for a specific tablet in this case. So if everything is blended up appropriately, you would expect it to perform uniformly from tablet to tablet to tablet. If there's heterogeneities [sic] in the system, you would imagine that something would fall apart odd or funny, so you would get a different release profile." Tr. 635:11-21 (Little Direct); see also Tr. 447:13-448:1 (Disman Depo). Dr. Kidane, one of the inventors of the Supernus Patents, also testified in his deposition that "[i]f there is inhomogeneity there would be variability in the dissolution profiles." Tr. 462:1-8 (Kidane Depo).

The results of Actavis's dissolution tests show low variability between tablets, which indicates that the Actavis Tablets "perform uniformly from tablet to tablet," as described by Dr. Little. Tr. 635:17-19 (Little Direct); PTX 39.8, 20, 32. Although the tablet is ultimately "destroyed," in the sense that it dissolves, during dissolution testing, see Tr. 716:12-20

(Little Cross), the Court is persuaded by Dr. Little's expert testimony that dissolution testing functions essentially as a proxy for tablet homogeneity by demonstrating that the tablets perform consistently with each other. See, e.g., Tr. 637:7-16 (Little Direct).

Finally, the Court finds that the results of the FDA-required uniformity testing confirm that Actavis's manufacturing process results in a uniform dispersion of ingredients and establish that the Actavis Tablets comprise a homogeneous matrix.

Chemical Imaging

In further support of its position that the Actavis Tablets comprise a homogeneous matrix, Supernus put forth evidence of chemical imaging of the Actavis Tablets.[15] Dr. Bugay testified at length regarding the Raman imaging tests he performed on the Actavis Tablets as well as the Oxtellar XR® tablets and his conclusions regarding the presence of a homogeneous matrix. Dr. Bugay explained that he was asked by the Plaintiff to examine the Actavis Tablets and the Oxtellar XR® tablets using Raman imaging to determine whether the pharmaceutical formulations of

[15] Supernus contends that the chemical images are "not necessary to show that Actavis's Tablets contain a homogeneous matrix," but that they are consistent with and confirm the other evidence demonstrating that the Actavis Tablets comprise a homogeneous matrix. Pl. Br. at 12. The Court agrees.

each of the tablets comprises a homogeneous matrix, as construed by the Court. Tr. 318:24-320:9 (Bugay Direct).

The first step of Dr. Bugay's analysis required microtomy of the tablets, which entails shaving the tablet samples to expose the interior of the tablets for analysis. Id. at 320:17-321:12. Dr. Bugay then performed Raman spectroscopy to determine what molecular compounds are present in the samples. This process results in a distinct Raman spectrum for each molecular compound that is present. Dr. Bugay testified that each compound's Raman spectrum is like a "unique fingerprint" that allows the experimenter to identify each individual constituent in a tablet sample and whether a particular area contains one or more of the constituents. Id. at 321:13-326:4.

This procedure was repeated for 35,000 data points on each tablet, covering roughly 70% of the tablet's surface. Id. at 326:5-13, 331:1-18. Dr. Bugay persuasively testified that it is crucial to examine as much of the tablet as possible in order to assess the homogeneity of the tablet matrix. Indeed, Dr. Bugay echoed Dr. Little's concern, supra, regarding the size of the tablet examined. On the other hand, Dr. Muzzio only examined 7-8% of the tablet surface. Tr. 396:12-20 (Bugay Cross). Scale is critically important in this analysis, as Dr. Muzzio readily admits. See Tr. 894:20-895:2 (Muzzio Direct) ("And so, for example, if I want to answer the question, is my batch uniform,

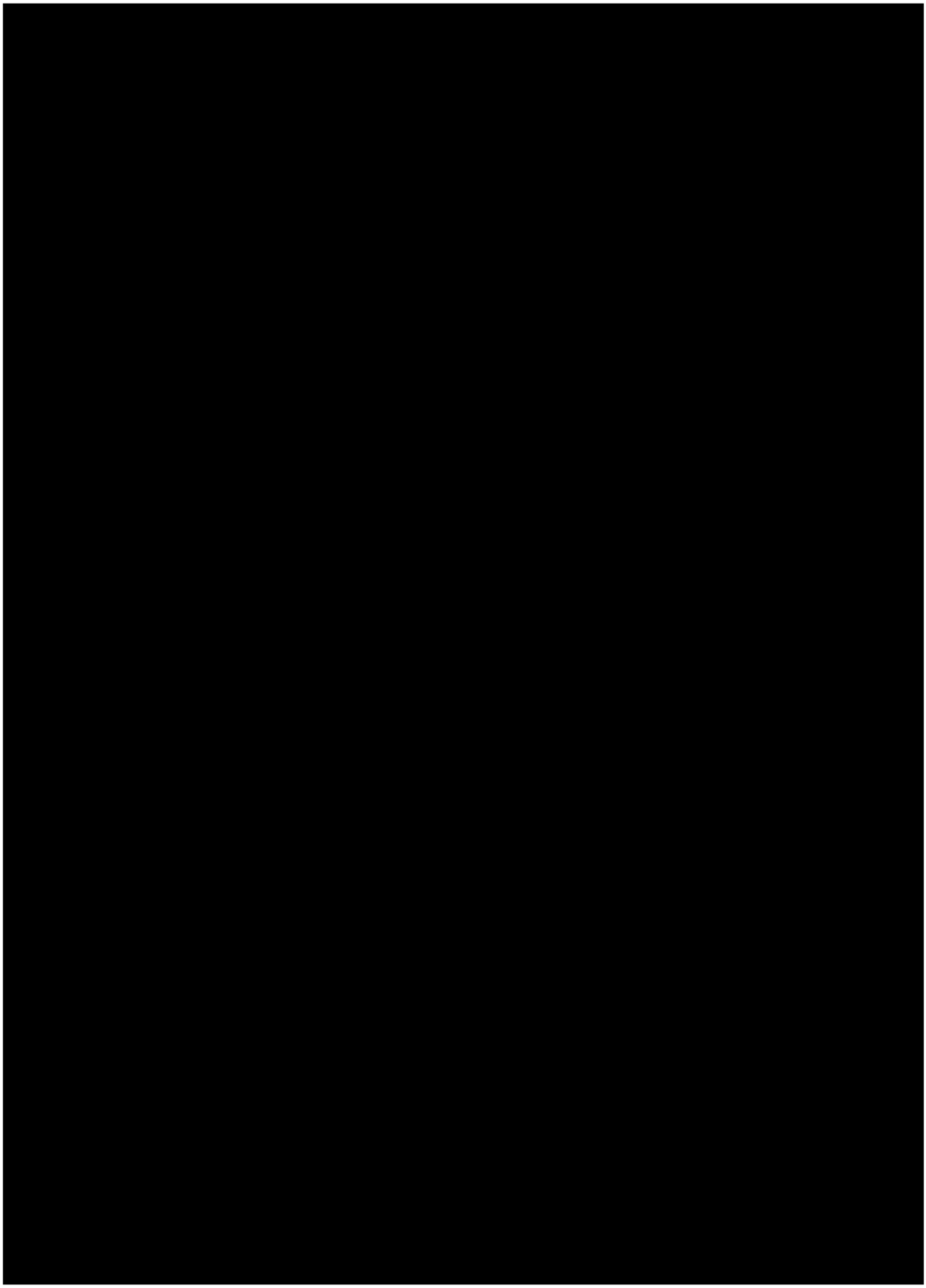
or is my blend uniform, then I'm going to use my blend to make tablets, so I have to use samples that are roughly the size of tablets, because the relevant scale at which I have to examine that blend is the tablets, because that's what I'm going to make with that blend. I'm going to make tablets. So that's the right scale of examination."); Tr. 964:7-25 (Muzzio Cross) (". . . there is always this issue of at which scale you're examining the structure . . . If you go down to atoms, nothing is homogeneous. . . . Well, what I said is that when you look to that scale, it would always look heterogeneous, right?"). Given the material importance of scale, the Court is persuaded that Dr. Bugay's chemical images, which examine the vast majority of the tablet surface, more accurately assess the homogeneity of the matrix.[16]

[16] Dr. Bugay's comparison of the chemical images to images of a person's head is likewise persuasive and helpful to this Court's assessment of the competing chemical images. In explaining that scale and perspective is crucial to this analysis, he gave the following analogy: "If I take a picture looking downward upon your head from a foot above, I see that you have hair and you have a full head of hair. If I bring that camera down to a different perspective to just above your scalp and I take a picture that goes between the hair follicles I would say you are bald. . . . And so without that context you can make this image say one thing or it makes you say another thing. In consideration of that, that's why I did my imaging with respect to as much of the tablet as possible so it's the right perspective that you are looking at as taught by Claim 1 of the patent." Tr. 395:6-23 (Bugay Direct).

By processing and compiling the thousands of data points, Dr. Bugay created color-coded Raman chemical images which indicate both the presence and the location of the various constituents in the tablet sample. Tr. 339:8-340:13 (Bugay Direct). Dr. Bugay then confirmed this data using extensive validation procedures. Id. at 346:1-349:1.

Raman chemical images of the Actavis Tablets were created that show the presence of oxcarbazepine, [redacted] act as element 1(b) matrix-forming polymers. PTX 253. Supernus argues that [redacted] also serves as an element 1(c) solubility enhancer. Actavis disputes this. [redacted], also known as [redacted] respectively, are element 1(d)s release promoting agent with pH-dependent solubility. [redacted], Supernus posits, is a release promoting agent that is not a polymer with pH-dependent solubility. The parties dispute whether this compound satisfies element 1(d).

Dr. Bugay also prepared Raman chemical images of the Oxtellar XR® tablets that show the presence of oxcarbazepine, MCC, HPMC, SLS, Methacrylic Acid Copolymer Type C, and PVP. PTX 280. The results of Dr. Bugay's Raman imaging on the Actavis Tablets and Oxtellar XR are as follows:



Dr. Bugay visually assessed the Raman chemical images and concluded that each of the constituents in the Actavis ANDA product is uniformly dispersed throughout the tablet and, therefore, that each tablet comprises a homogeneous matrix.[17] Tr. 340:25-342:6 (Bugay Direct). The constituents are not localized in one area alone, but rather are found throughout the tablet surface. While the constituents are admittedly not meticulously arranged in the tablet, Dr. Bugay explained that there are limitations when it comes to molecular compounds. Tr. 341:20-23 (Bugay Direct) ("The objective of formulators in generating or creating a pharmaceutical manufacturing process is to create, okay, a consistent homogeneous product, okay? Do we get it perfect? No. We have limitations in that."). A person of ordinary skill in the art would understand that molecules cannot be perfectly lined up by a formulator the way that bricks

[17] The Defendants insist that Dr. Bugay employed a "quadrant theory" to evaluate the Raman chemical images and determine uniformity. Dr. Bugay denied the use or existence of any such theory and clarified that he used the term "quadrant" only to describe the mental process of visually assessing the images. As part of his visual assessment, he determined whether there was localization of any excipients in a particular quadrant of the image. If there had been such localization, then he would immediately conclude that the excipients were not uniformly dispersed. Since he did not encounter any such localization, he then continued to visually inspect each section of the image in smaller sections to assess uniformity. Tr. 373:23-375:6 (Bugay Cross). The Court agrees with Supernus and Dr. Bugay that there is no "quadrant theory" per se. Dr. Bugay was merely attempting to explain how he visually inspected the images.

can be exactly laid out by a mason. Id. at 341:14-23. This is consistent with Dr. Little's testimony at the Markman hearing, as outlined supra.

In Dr. Bugay's expert opinion, homogeneity in this context is measured by lack of localization. Id. at 341:5-342:6 ("If we go back to the oxcarbazepine image for a minute, as you look at this, I don't see that the active here is localized in one area. . . . I see that the pixels are dispersed throughout the entire image. . . . given my pharmaceutical experience, 30 years of looking at tablets and such, I look at that as being uniformly dispersed."). Dr. Bugay's explanation of how a person of ordinary skill in the art would understand homogeneity and uniformity in this context is illustrative and merits reproduction here in full:

> I look at this in the context of a person skilled in the art of pharmaceutical analysis. Okay? And so we know that we cannot get a perfect uniform distribution, as I mentioned today, like a mason doing a herringbone pattern or doing end-to-end blocks in a brick wall. Okay? Yet we do know we wish to have the constituents dispersed through the tablet. We know that individuals snap a tablet in half and take half in the morning and half in the evening, and we don't want all the API [active pharmaceutical ingredient] to be over in that one half because later in the day they don't get their medication.
>
> And so when we look at this term, it's uniformly dispersed, we look at that knowing that we can't have the perfect brick pattern, yet we do know we want those constituents to be dispersed throughout that tablet matrix, and by the design or the experiments that I did, namely, the preparation, the Raman

> imaging, and then the interpretation and seeing that there wasn't localization here or there, that led to my opinion, in the context of the pharmaceutical manufacturing process and my experience, that it was uniformly dispersed.

Tr. 373:3-22 (Bugay Cross).

Dr. Muzzio agreed in substance with Dr. Bugay's measure of homogeneity. Dr. Muzzio testified that, per the Court's construction of "homogeneous matrix," "you have to have [a] substantially uniform amount of each ingredient in each location of the tablet." Tr. 893:8-17 (Muzzio Direct).

Further, Dr. Little agreed with Dr. Bugay's assessment of the Raman images. He testified that the Raman chemical images of the Actavis Tablets demonstrate that all the constituents are found in all areas of the tablet. None are isolated or segregated in, for example, just the coating or the core of the tablet. Tr. 638:23-639:17 (Little Direct). In his expert opinion, this establishes that each Actavis Tablet comprises a matrix in which all of the constituents are uniformly dispersed.

Defendants make much to do about the fact that Dr. Bugay was unable to create a Raman chemical image demonstrating the presence and location of [redacted] in the Actavis Tablets. See, e.g., Defendants' Post-Trial Brief ("Defs. Br.") at 4 [Docket No. 391]; Tr. 358:7-15, 359:21-361:1 (Bugay Cross). Dr. Bugay testified that he was unable to do so, even though it is undisputed that [redacted] is present in the Actavis Tablets,

PTX 116.6, due to the low concentration of [redacted] in the Actavis Tablets. Tr. 359:21-361:1 (Bugay Cross). Dr. Bugay explained, however, that it is possible that [redacted] would have been present in larger concentrations in a different cross-section or "slice" of the tablet. Id. at 360:4-361:1; Tr. 351:22-352:15 (Bugay Direct). He likened this to an "iceberg effect," wherein the quantity shown in the image may depend on where on the "iceberg" he sliced. Tr. 344:3-16 (Bugay Direct); Tr. 412:3-18 (Bugay Cross) (". . . when we slice through a tablet, we know for a fact that we don't slice through the equator of every single constituent that's in the tablet."). The fact that the excipients all went through the same manufacturing process, coupled with the data supporting uniform dispersion of the other constituents, allowed Dr. Bugay to conclude that [redacted] is also uniformly dispersed throughout the Actavis Tablet. Tr. 352:17-353:3 (Bugay Direct). The Court finds this explanation credible and persuasive.

Similarly, although Dr. Bugay only tested the 600 mg Actavis Tablets, in his expert opinion, the 150 mg and 600 mg tablets also comprise homogeneous matrices in which all the constituents are uniformly dispersed since each tablet is created through the same manufacturing process. The only

difference is in the amount of each constituent.[18] This does not affect the homogeneity of the tablets. Id. at 353:7-17. Additionally, Dr. Bugay testified that the objective of any formulator creating a standard pharmaceutical formulation is to achieve a homogeneous matrix. Id. at 341:20-22; Tr. 361:13-18 (Bugay Cross).

On cross-examination, Dr. Bugay was presented with the Raman chemical images for both the Actavis Tablet and the Supernus Oxtellar XR® tablet. Dr. Bugay refused to compare the uniformity or homogeneity of the two tablets to each other, correctly noting that the two tablets should not be compared to each other. Rather, the tablets should each be compared to the claims of the relevant patents. Tr. 376:19-377:19 (Bugay Cross). Dr. Bugay's testimony on cross-examination is enlightening:

> In addition, why are we comparing Oxtellar -- excuse me Oxtellar XR® with a different process of producing it than the Actavis product? My understanding of this process is that I looked at determining whether a homogeneous matrix existed, based upon comparing the Actavis product to the elements of Claim 1. Not a comparison test between Actavis versus Supernus's product. It wasn't a comparison test to this -- to this unknown, okay? They are made differently. Their particle sizes are differently [sic]. That means that as they come out of the process, there's [sic] going

[18] This is supported by Actavis's request for an ***in vivo*** bioequivalence waiver from the FDA which states there is "formulation proportionality" and that the data for the 600 mg tablets may be extrapolated to the 150 mg and 300 mg tablets. PTX 97.3.

> to be differences. But what's most important is that as you look at it -- Counsellor, do you see a localization in the bottom image of all the pixels being to the upper right-hand side? No. We see those blue pixels dispersed throughout an entire two-dimensional area. . . . And so because of that, and because we understand we don't have a perfect process, we are trying to achieve it, we see that it is dispersed there.

Id. at 376:19-377:12.

While Actavis is correct that "[o]ur case law does not contain a blanket prohibition against comparing the accused product to a commercial embodiment," Adams, 616 F.3d at 1288, the Court nonetheless finds that Actavis is improperly attempting to limit the term "homogeneous matrix" to what is seen in Oxtellar XR®. The Adams court held that "when a commercial product meets all of the claim limitations, then a comparison to that product may support a finding of infringement." Id. at 1289 (emphasis added). Other Federal Circuit precedent, however, makes clear that a defendant may not prove non-infringement merely by comparing its accused product to a commercial embodiment of the patentee's invention. See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1347 (Fed. Cir. 2003) (vacating finding of non-infringement because "the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment."); Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1423 (Fed. Cir. 1994)

("As we have repeatedly said, it is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent."); SDS USA Inc. v. Ken Specialties Inc., 122 F. Supp. 2d 533, 539 (D.N.J. 2000) (collecting cases).

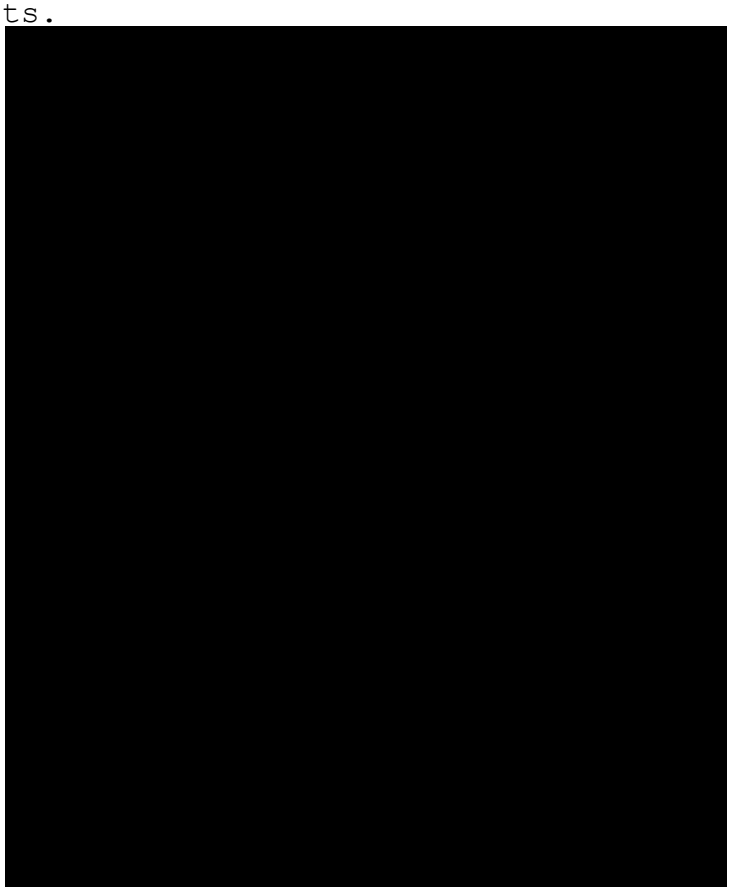
Actavis's expert, Dr. Muzzio, willingly compared what Dr. Bugay would not. He testified that the Raman images of the Actavis Tablet "show[ed] lack of homogeneity" because the oxcarbazepine particles were often "lumped together, agglomerated." Tr. 900:13-25 (Muzzio Direct). The Supernus tablet, on the other hand, "comes much closer, in [his] mind, to what [he] would consider a homogeneous matrix. . . . It seems to have a very close to uniform distribution." Id. at 901:11-15. He formed his conclusions regarding homogeneity not by comparing Actavis's ANDA product to the Patents-in-Suit, but to the commercial embodiment, Oxtellar XR®. See id. at 901:21-902:5 ("Well, in my opinion, again looking at this from the perspective of how I understand the claim construction provided by the court, on the left I see Actavis having a tablet where, as I said, the drug is lumped into agglomerates containing many types of particles each and there's hardly any drug at all and there's a variation as I move from left to right. In comparison I see the Supernus distribution of the drug being very uniform,

probably as close to completely uniform as I would expect something could be where there's drug everywhere."); Tr. 960:2-8 (Muzzio Cross) ("It's [Oxtellar XR®] much more homogeneous by a significant degree than what I see in the Actavis matrix.").

Dr. Muzzio also performed his own Raman imaging to create three dimensional Raman images for the Actavis Tablets and Supernus's Oxtellar XR® tablets. DTX 495. Comparing the three dimensional Raman images for the Actavis and Supernus tablets, he testified that, in the Supernus tablets, "there is a much more intimate distribution of – a much more homogeneous distribution of ingredients. . . . the degree of commingling is much, much more intimate" than in the Actavis Tablets. Tr. 909:9-18 (Muzzio Direct). Dr. Muzzio came to this conclusion from an analysis of merely 1/15th of the Actavis Tablet, compared to Dr. Bugay's analysis of 70-80% of the tablet. Tr. 990:5-991:24 (Muzzio Cross). The cross-examination of Dr. Muzzio effectively demonstrated what Dr. Muzzio had previously explained was critically important, namely the question of scale. See id. at 992:3-993:2. When focusing on solely a 1/15th section of Dr. Bugay's Raman image showing the presence and location of SLS in the Oxtellar XR® tablet, the distribution of SLS seems anything but uniform. Yet, the parties agree that each Oxtellar XR® tablet as a whole comprises a homogeneous matrix comprising, in part, SLS. This is demonstrated by

assessing the entirety of Dr. Bugay's Raman image. See PTX 280.12; Tr. 992:3-993:2 (Muzzio Cross).

Similarly, Dr. Muzzio's Near Infrared ("IR") imaging of the Actavis and Supernus tablets shows the presence of oxcarbazepine throughout the tablets. DTX 493. Although the Near IR image of the Actavis Tablet shows areas that have a high concentration of oxcarbazepine and other areas that have a comparatively low concentration of oxcarbazepine, see Tr. 912:17 (Muzzio Direct), Dr. Muzzio conceded that "the two halves don't look very different from each other." Id. at 913:23-24. This, too, confirms that there is no localization of constituents in the Actavis Tablets.



DTX 493 at p. 9.

Although it can be said that the constituents are dispersed "more" uniformly in the Supernus Oxtellar XR® tablets than the Actavis Tablets, this has no bearing on whether the Actavis Tablets comprise a homogeneous matrix. In fact, despite making these comparisons, Dr. Muzzio admits that "there are degrees of homogeneity." Tr. 904:11 (Muzzio Direct).[19] Thus, the Court finds that the chemical imaging confirms that both tablets comprise a homogeneous matrix, even if, when compared to each other, the dispersion of the constituents may be considered more uniform in one than the other.[20] It is irrelevant whether the Actavis Tablets are "less homogeneous" than the Oxtellar XR® tablets.[21] In sum, the Court holds that the Actavis Tablets

---

[19] Dr. Muzzio's testimony in comparing the Near IR images illuminates the fact that homogeneity exists in degrees. Tr. 914:19-24 (Muzzio Direct).

[20] Although the Defendants urge the Court to rely primarily on the chemical images to establish that the Actavis Tablets do not comprise a homogeneous matrix, the Court, like Dr. Muzzio, "hesitate[s] to put too much emphasis just on pictures," Tr. 1043:1-2 (Muzzio Cross), and does not. See supra footnote 14.

[21] This point was made all the more clear when the parties began quibbling over whether a matrix is "very" or "quite" homogeneous. See Tr. 962:14-23 ("Q. Now you, yourself, acknowledge, do you not, that the Supernus product is very homogeneous? A. I think that the matrix in the Supernus tablets is quite homogeneous, yes. Q. Well, my question is, haven't you – haven't you given the opinion that the Supernus tablets are very homogeneous? A. There's a difference between "quite" and "very"?"), 964:2-6 ("Q. So earlier, you said it's most homogeneous, it's more homogeneous, it's closer – it's practically close to what – I don't know, what's perfect or something, but what is it? Is it very homogeneous or is it just more homogeneous than Actavis?") (Muzzio Cross).

comprise a homogeneous matrix, as construed by this Court and as understood by a person of ordinary skill in the art.

(2) Agent that Enhances the Solubility of Oxcarbazepine

Supernus contends that two compounds in the Actavis ANDA tablets satisfy element 1(c) of Claim 1, which requires "at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents." '898 Patent, Claim 1(c). According to the Plaintiff, two excipients in the Actavis ANDA tablets, [redacted] and [redacted] (also known as [redacted]), the particular grade of HPMC in the Actavis Tablets, constitute agents that enhance the solubility of oxcarbazepine.[22] See,

[22] Supernus also moved in limine to preclude Actavis from arguing that its ANDA tablets lack an element 1(c) agent that enhances the solubility of oxcarbazepine because this position was not disclosed by Actavis in its non-infringement contentions as required by Local Patent Rule 3.6(e) [Docket No. 327]. The Court denied the motion without prejudice [Docket No. 355]. The motion was renewed by Plaintiff at trial. The Court holds that there was no prejudice or surprise to Supernus, given that Supernus was aware of Actavis's position since, at the very latest, February 9, 2015 when Actavis denied its admission request regarding the presence of an element 1(c) agent that enhances the solubility of oxcarbazepine. Furthermore, Supernus has pursued and engaged in discovery on this claim element since late 2013. Given the centrality of element 1(c) in the parties' discovery and motion practice, as well as the litigation as a whole, the Court denies the Plaintiff's motion, once again, with prejudice.

e.g., Tr. 642:14-644:2 (Little Direct); Tr. 293:15-22 (Chyall Direct). The Court will address [redacted] first.

Dr. Leonard Chyall, Supernus's expert in analytical testing of pharmaceutical compositions, performed solubility tests on oxcarbazepine in the presence of [redacted]. Tr. 282:20-287:2 (Chyall Direct). He did not, however, run any solubility or dissolution tests on the Actavis Tablets themselves. Tr. 297:1-8 (Chyall Cross).

In performing the solubility tests, Dr. Chyall first prepared four solutions with varying percent concentrations of [redacted] to test what solubility enhancing effect, if any, [redacted] has on oxcarbazepine. The four solutions contained 0% [redacted] (control), 1% [redacted], 5% [redacted], and 10% [redacted]. After placing oxcarbazepine in the various [redacted] solutions and agitating the materials overnight, Dr. Chyall used a high pressure liquid chromatography ("HPLC") test to measure how much oxcarbazepine dissolved in the solution. Tr. 283:13-284:2, 285:6-287:2 (Chyall Direct). Dr. Chyall's testing presented the following results:

[redacted]

PTX 285.1.

The results of Dr. Chyall's HPLC tests indicate that as the concentration of [redacted] increases, so does the solubility of oxcarbazepine. Tr. 292:20-293:22 (Chyall Direct). Dr. Chyall persuasively testified that [redacted] is an agent that enhances the solubility of oxcarbazepine, as required in element 1(c) of Claim 1. Id.

Dr. Little, relying in part on Dr. Chyall's solubility testing, also concluded [redacted] acts in the Actavis Tablets as an agent that enhances the solubility of oxcarbazepine. He also relied upon the relevant patent claims and specifications, the patent prosecution history, peer-reviewed literature, product literature for [redacted], and Actavis's manufacturing process and batch records to come to this conclusion. Tr. 643:8-14, 651:2-20 (Little Direct).

A reading of the patent specifications supports this conclusion. The specifications for the '898 Patent state that the "[s]olubilizers preferred in this invention include . . . complexing agents such as low molecular weight polyvinyl pyrrolidone [PVP] . . ." '898 Patent, col. 5, ll. 9-15. The Supernus Patents clearly contemplate PVP, the generic term for Kollidon, as a solubilizer. The fact that the "preferred" solubilizer is a low molecular form of Kollidon is of no moment. Nothing in the patent or its specifications limits the solubilizers to these "preferred" types. See, e.g., Tr. 645:6-

20 (Little Direct). In fact, Dr. Little testified that the molecular weight does not impact the ability of the compound to create a complex, as required by the Patents-in-Suit. Id. He further testified that "low molecular weight" is a relative term. While he would not necessarily characterize [redacted] as a low molecular weight PVP, there are PVP grades with much higher molecular weight than [redacted]. Tr. 689:13-17 (Little Cross).

Moreover, in addressing the prior art, the Patent Examiner identified another patent which disclosed a pharmaceutical formulation comprising several constituents, including polyvinyl pyrrolidone. PTX 5.385. After polyvinyl pyrrolidone, the patent examiner added a note in parentheses: "(a surface acting agent; at least one agent that enhances the solubility of oxcarbazepine; that polyvinylpyrrolidone is known in the art as a surface active agent, . . .)." Id.

Even the product brochure issued by BASF, the company that supplies Actavis with its [redacted], states that [redacted] "can also be deployed to modify the viscosity of liquid dosage forms and improve the bioavailability of certain poorly soluble actives." PTX 306.6; Tr. 650:5-20 (Little Direct). Likewise, the Handbook of Pharmaceutical Excipients, relied upon by Dr. Little, explains that "Povidone is used as a solubilizer . . . and has been shown to enhance dissolution of poorly soluble

drugs from solid-dosage forms." PTX 292.22; Tr. 651:21-653:3 (Little Direct). It is well-established that oxcarbazepine is a poorly soluble active ingredient. See, e.g., Tr. 650:12-14 (Little Direct); Tr. 61:1-7 (Bhatt Direct). Dr. Little testified that both the [redacted] brochure and the Handbook of Pharmaceutical Excipients are consistent with his conclusion that [redacted] enhances the solubility of oxcarbazepine. Tr. 650:15-20 (Little Direct).

While the Defendants insist that [redacted] is merely a "binder" and not an agent that enhances the solubility of oxcarbazepine, the functions listed in Actavis's ANDA are merely proposed functions and a single compound may have several functions. See, e.g., Tr. 606:4-16 (Little Direct). The Court agrees with the Plaintiff's position that just because "Actavis is smart enough not to say we have a solubility enhancer in the form of PVP" does not mean that it is not in practice a surface active agent that enhances the solubility of oxcarbazepine. Tr. 861:15-21. Dr. Little persuasively explained this.

To prove that there is no solubility enhancing agent in its ANDA tablets, the Defendants also rely on a letter from the FDA to Actavis in response to Actavis's bioequivalence study report, which reads: [redacted]

[redacted] PTX 54.4.

Yet, rather than address [redacted], as the FDA requested, [redacted] PTX 41.8. Dr. Harold Hopfenberg, Actavis's expert witness, testified and the Court agrees that this [redacted] must be a reference to [redacted] since that is the only [redacted] listed in the chart in Actavis's ANDA outlining the composition of its generic tablets. Tr. 1483:2-15 (Hopfenberg Cross). Dr. Hopfenberg further testified that increasing the wettability of an active ingredient by reducing the contact angle is one way in which a surface active agent works. Id. at 1484:13-17; see also Tr. 1475:8-10 (Hopfenberg Cross); PTX 235.3 (defining surface active agent and noting that "there are three categories of surface active agents: detergents, wetting agents, and emulsifiers) (emphasis added). The Court observes that element 1(c) of the Supernus Patents requires "at least one agent that enhances the solubility of oxcarbazepine selected from the group

consisting of surface active agents" and others. '898 Patent, col. 12, ll. 60-63.

Given the extensive expert testimony from Dr. Little and Dr. Chyall, Dr. Chyall's solubility testing, and the scientific literature available, the Court concludes that [redacted] acts as an agent that enhances the solubility of oxcarbazepine in the Actavis Tablets. The Actavis Tablets, therefore, comprise an element 1(c) solubility enhancing agent in the form of [redacted]

The Court does not agree with the Defendants' argument that the "examples in the specification also directly support the conclusion that HPMC and PVP are not solubility enhancers." Defs. Br. at 14 (emphasis in original). Table 1 recites the composition of three "non-enhanced" oxcarbazepine formulations that contain "no solubility/release enhancer." '898 Patent, col. 2, ll. 60-62, col. 9, ll. 11-37. Only the CR-M formulation contains [redacted] and only the CR-S formulation contains [redacted]. None of the non-enhanced formulations contain a release promoter. Table 4 lists the composition of one enhanced and one non-enhanced oxcarbazepine formulation. Id. at col. 10, l. 56-col. 11, l. 15. The non-enhanced formulation is described in the Supernus Patents as one "without solubility enhancer." Id. at col. 3, ll. 14-17. [redacted] is not present in either of the formulations in Table 4. [redacted] is present in

both. Notably, however, [redacted], a release promoter, is only present in the enhanced formulation.

The Supernus Patents clearly state that a "combination of solubility and release promoters is contemplated in this invention." Id. at col. 4, ll. 14-17. The description of Table 1 states that the non-enhanced formulations contain no "solubility/release enhancer," referring, in this Court's opinion, to the combination of solubility and release promoters required in the invention. This is confirmed by Dr. Bhatt's testimony that solubility enhancing agents alone were insufficient and that a release promoter was also required. Tr. 75:11-17 (Bhatt Direct) (". . . the tablets needed more porosity to allow the fluid, the media, to go into the tablet and dissolve or help dissolve the drug along with the solubility enhancer.").

Likewise, the non-enhanced formulation in Table 4 does not contain a combination of solubility enhancing and release promoting agents, while the enhanced formulation has both. To the extent that the description of the non-enhanced formulation in Table 4 is not referring to the combination of solubility and release promoters, the Court still finds it irrelevant to its analysis of whether [redacted] satisfies claim element 1(c) as it is not present in either of the formulations in Table 4. The Plaintiff is correct that "the patents never expressly describe

a [redacted]-containing formulation as 'without solubility enhancer.'" Plaintiff's Responsive Post-Trial Brief ("Pl. Resp. Br.") at 13 [Docket No. 408].

Supernus claims that, in addition to [redacted], [redacted] also acts as an element 1(c) solubility enhancing agent in the Actavis Tablets. The Court, however, disagrees and finds that Supernus has not established by a preponderance of the evidence that [redacted] is an agent that enhances the solubility of oxcarbazepine, such that it satisfies claim element 1(c) of the Supernus Patents.

Dr. Chyall was unable to run comparable solubility tests on [redacted]. He testified that [redacted] is not amenable to the solubility testing he performed because the highest [redacted] concentration solution that he could achieve was 1%. Tr. 287:3-19 (Chyall Direct). While he was able to run solubility tests using solutions with very low concentrations of [redacted] all below 1%, Dr. Chyall concluded that the solubility enhancing differences between the varying concentrations amounted to experimental error. Id. at 287:13-19; Tr. 298:21-299:5 (Chyall Cross). Dr. Chyall reached no conclusions about the solubility enhancing effect of [redacted] on oxcarbazepine. Tr. 298:5-6 (Chyall Cross).

Dr. Little, however, concluded, after reviewing peer-reviewed literature, product literature for [redacted], and

Dr. Bugay's Raman chemical images, that [redacted] is an agent that enhances the solubility of oxcarbazepine. See, e.g., Tr. 653:4-7 (Little Direct). As with [redacted], the specifications identify "low molecular weight hydroxypropl methyl cellulose [HPMC]" as a preferred solubilizer. '898 Patent, col. 5, ll. 9-16. Nothing in the Patents-in-Suit or the specifications limits the solubilizing agent to the non-exhaustive listed of "preferred" solubilizers.

The [redacted] brochure issued by Dow, the company which supplies Actavis with its [redacted] for use in its generic tablets, explains that "Methocel products act as surfactants," which are also known as surface active agents. PTX 309.5; Tr. 655:1-11 (Little Direct). It is well-established in the peer-reviewed literature that "HPMC possesses surface active properties." PTX 294.3; Tr. 655:18-656:3 (Little Direct). Another peer-reviewed article states that HPMC "possesses a significant solubilizing effect which is due to the formation of a water soluble drug-polymer complex." PTX 295.2; Tr. 654:5-10 (Little Direct). However, this article discussed a different active ingredient called piroxicam. Id. While this article may establish that HPMC is an agent that enhances the solubility of piroxicam, it tells the Court nothing with regard to whether it has the same solubilizing effect on oxcarbazepine.

Dr. Little testified that the literature he reviewed about HPMC was consistent with his understanding, based on his years of experience as chemical engineer, that [redacted] is a surface active agent. Tr. 656:2-3 (Little Direct). Dr. Little also concluded that [redacted] can also act as a hydration promoting agent, as described in element 1(c) of Claim 1. HPMC is a hydrophilic compound that draws water into a formulation, causing the formulation to swell dramatically. Id. at 656:4-13. Dr. Little testified that Dr. Bugay's Raman chemical images, showing that HPMC and oxcarbazepine are co-located in the Actavis Tablets, confirm this conclusion. Id. at 656:14-657:4; PTX 253.17. This co-location of HPMC and oxcarbazepine in the Raman images of the Actavis Tablets is the only evidence that relates to [redacted] impact on oxcarbazepine.

Although the expert testimony and the scientific literature suggests that [redacted] may enhance the solubility of certain compounds, there is insufficient evidence in the record to establish by a preponderance of the evidence that [redacted] enhances the solubility of oxcarbazepine. In fact, Dr. Hopfenberg testified that he "found nothing in the literature . . . that demonstrated that there was an affect [sic] of solubilization provided by [redacted], the specific grade [in the Actavis Tablets] and oxcarbazepine. I've seen no experiments that would be consistent with the conclusion that [redacted]

would solubilize oxcarbazepine." Tr. 1363:3-9 (Hopfenberg Direct). Furthermore, Dr. Chyall's solubility tests, which demonstrated that [redacted] enhances the solubility of oxcarbazepine, were inconclusive with regards to [redacted].

Dr. Bhatt explained that explained that excipient compatibility studies are essential because "[e]very drug molecule is unique in its own right. Just because we have used component A in a previous drug product does not guarantee that that component is going to be acceptable in a project that's using drug B." Tr. 71:24-72:3 (Bhatt Direct). As Dr. Bhatt astutely observed, "[o]xcarbazepine . . . is a chemical with its own properties. It has its own physical properties, and it behooves us as good scientists to study even standard excipients to ensure that those standard, quote/unquote, standard excipients are going to be compatible with the drug at hand, which is oxcarbazepine." Id. at 72:4-9.

Element 1(c) of Claim 1 specifically calls for an agent that enhances the solubility of oxcarbazepine. Given the lack of evidence regarding the solubility enhancing effect of [redacted] on oxcarbazepine, this Court will not consider [redacted] as satisfying element 1(c) of Claim 1 of the '898 Patent.

In sum, the Court holds that the Actavis Tablets infringe Claim 1 of the '898 Patent and Claim 1 of the '131 Patent.

Actavis's ANDA product is admittedly a pharmaceutical formulation for once-a-day administration of oxcarbazepine for the treatment of seizures. This Court has found that Actavis's ANDA product additionally comprises a homogeneous matrix comprising oxcarbazepine (element 1(a)), [redacted] (element 1(b)), [redacted] (element 1(c)), and [redacted] (element 1(d)).

d) The Dependent Claims

Having established that the Actavis Tablets infringe Claim 1 of the '898 and '131 Patents, the Court now turns to the dependent claims. See Monsanto Co. v. Syngenta Seeds, Inc., 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting Wahpeton Canvas Co., Inc. v. Frontier, Inc., 870 F.2d 1546, 1552 n. 9 (Fed. Cir. 1989) ("One may infringe an independent claim and not infringe a claim dependent on that claim.").

(1) The Pharmacokinetic Claims of the '898 and '131 Patents

Claims 6, 7, and 8 of the '898 and '131 Patents were evaluated at trial as a group called the pharmacokinetic or "PK" claims. Claim 6 and 7 depend upon Claim 1 and Claim 8 depends upon Claim 7.

The PK Claims of the '898 Patent read:

> 6. The pharmaceutical formulation of claim 1, wherein the amount of oxcarbazepine is effective to produce a

> steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 10 µg/ml.
>
> 7. The pharmaceutical formulation of claim 1, wherein the formulation is effective in minimizing fluctuations between C_{min} and C_{max} of monohydroxy derivative of oxcarbazepine.
>
> 8. The pharmaceutical formulation of claim 7, which provides C_{max} levels of monohydroxy derivative of oxcarbazepine in the range of about 6 µg/ml to about 10 µg/ml and C_{min} levels of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 5 µg/ml.

The PK Claims of the '131 Patent are nearly identical and read:

> 6. The method of claim 1, wherein the amount of oxcarbazepine is effective to produce a steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 10 µg/ml.
>
> 7. The method of claim 1, wherein the formulation is effective in minimizing fluctuations between C_{min} and C_{max} of monohydroxy derivative of oxcarbazepine.
>
> 8. The method of claim 7, which provides C_{max} levels of monohydroxy derivative of oxcarbazepine in the range of about 6 µg/ml to about 10 µg/ml and C_{min} levels of monohydroxy derivative of oxcarbazepine in the range of about 2 µg/ml to about 5 µg/ml.

Supernus retained Dr. Dhiren Thakker, a pharmacokinetics and pharmacodynamics expert, to compare the pharmacokinetics of the Actavis Tablets to the limitations of the PK Claims. To do so, Dr. Thakker used the MHD blood levels data for the 600 mg tablets included in the bioequivalence study report submitted by Actavis to the FDA. Tr. 532:5-533:8 (Thakker Direct); PTX 104. This data simply reflected the MHD levels over time in the

subjects after one dose of the Actavis ANDA product. Tr. 533:1-11 (Thakker Direct). He then used a superposition analysis to project what the MHD blood levels would be after multiple dosages. This involved adding an additional curve at every dosage interval, i.e. since the Actavis Tablets are for once daily administration, an additional curve was added every twenty-four hours. Id. at 533:12-535:3. By continuing to add curve until C_{min} and C_{max} stabilized, Dr. Thakker was able to determine steady state blood level. Id. Dr. Thakker credibly testified that this is a well-established method and common industry practice used to calculate and project plasma levels for multiple dosing of various products. Id. Actavis's expert in pharmaceutical sciences, Dr. Michael Mayersohn, likewise utilized this methodology. See Tr. 1075:12-16, 1081:14-24 (Mayersohn Direct).

The Defendants attempt to discredit Dr. Thakker because he was only able to calculate the steady state blood levels for thirty-six of the forty-one subjects in Actavis's study. Tr. 553:25-559:2 (Thakker Cross). Dr. Thakker explained that there was insufficient data available to calculate the terminal elimination rate constant, which is a necessary figure for conducting a superposition analysis. Tr. 537:20-538:22 (Thakker Direct). Dr. Thakker had no concerns about this. Id. at 538:23-539:3. Further, it appears that Actavis similarly had no

concerns about the insufficient test data for these five subjects. In its bioequivalence study report submitted to the FDA, from which Dr. Thakker obtained the data for his superposition analysis, Actavis listed the data from these same five subjects as "missing." Tr. 591:10-595:25 (Thakker Redirect); PTX 104.764.

After conducting a superposition analysis on the 600 mg Actavis Tablet, Dr. Thakker determined that the C_{min} is [redacted] µg/ml and the C_{max} is [redacted] µg/ml. Tr. 539:9-14 (Thakker Direct). He concluded, therefore, that the MHD steady state blood level for this dose of the Actavis ANDA product falls within the limitations of Claim 6 of the '898 and '131 Patents. Id. at 539:15-22.

Dr. Thakker also concluded that the 600 mg Actavis Tablets are effective in minimizing fluctuations between C_{min} and C_{max} of MHD. Id. at 539:23-540:4. In this context, in Dr. Thakker's expert opinion, minimizing fluctuation requires the ratio of C_{min} to C_{max} to be at least 20%. He developed this understanding by looking at the patent specification, which provides an example of a pharmaceutical formulation that minimizes fluctuations between C_{min} to C_{max} where the steady state MHD levels are between 2 and 10 µg/ml. Id. at 540:5-23; '898 Patent, col. 5, ll. 41-46. According to Dr. Thakker's superposition analysis, the ratio of C_{min} to C_{max} is [redacted] or roughly [redacted]%. Dr. Thakker

concluded that the 600 mg Actavis Tablet likewise satisfies the limitations of Claim 7 of the '898 and '131 Patents. Tr. 539:23-540:4 (Thakker Direct).

The C_{min} and C_{max} figures that Dr. Thakker reached using superposition analysis also led him to the conclusion that the 600 mg Actavis Tablet satisfies the limitations of Claim 8 of the '898 and '131 Patents. The C_{min} [redacted] µg/ml is within the claim limitation, which requires the C_{min} to be between 2 and 5 µg/ml. The C_{max} [redacted] µg/ml is also within the claim limitation, which requires the C_{max} to be between 6 and 10 µg/ml. Id. at 540:24-541:12.

Although no clinical data regarding the 150 mg and 300 mg Actavis Tablets was available, Dr. Thakker was able to extrapolate the steady state C_{min} and C_{max} values for these tablets using simple arithmetic. Id. at 541:18-542:12. He simply quartered and halved the C_{min} and C_{max} values for the 600 mg to determine the C_{min} and C_{max} values for the 150 mg and 300 mg tablets, respectively. Id. at 542:3-7. Dr. Thakker testified that this was an appropriate method for determining the steady state MHD blood levels for the 150 mg and 300 mg tablets "because the pharmacokinetics for MHD are – you know, are linear with dose, in other words, they are proportional to dose, and this was already indicated by Actavis in their application. So I basically took that information and I just did a simple

arithmetic operation." Id. at 542:7-12. Moreover, Actavis requested an ***in vivo*** bioequivalence waiver from the FDA for the 150 mg and 300 mg tablets in light of the data obtained from the 600 mg tablets. PTX 97.3. This, too, supports Dr. Thakker's conclusion. Tr. 544:16-545:5 (Thakker). Actavis's own expert, Dr. Mayersohn agrees that MHD plasma concentration is "a linear system. And a linear system simply means that there is proportionality. If I were to double the dose, I would double the concentration." Tr. 1084:22-25 (Mayersohn Direct).

The Court is not troubled, as Actavis is, by the lack of ***in vivo*** data for the 150 mg and 300 mg tablets. Dr. Thakker testified persuasively as to the propriety of his calculations and methodology. Furthermore, if Actavis is able to rely upon ***in vivo*** data for the 600 mg tablets, including data related to MHD blood levels, to support bioequivalence of the 150 mg and 300 mg tablets, Actavis cannot fairly argue that Supernus cannot do the same. Similarly, the Court takes no issue with relying upon the results of a fasted study, as opposed to a fed study. Actavis's draft labeling text for its ANDA tablets explicitly states that extended release oxcarbazepine should be taken on an empty stomach. PTX 98.6.

The C_{min} and C_{max} for the 300 mg tablets are [redacted] µg/ml and [redacted] µg/ml, respectively. Tr. 545:12-15 (Thakker Direct). This falls within the limitations of Claim 6 of the '898 and '131

Patents. The ratio of C_{min} to C_{max} is also [redacted]%, which fulfills the limitation of "minimizing fluctuations" between C_{min} and C_{max} found in Claim 7 of the '898 and '131 Patents. However, the C_{max} of [redacted] µg/ml does not satisfy Claim 8 of the '898 and '131 Patents. Supernus concedes that it does not assert infringement of Claim 8 of the '898 and '131 Patents by the 300 mg dosage strength of the Actavis Tablets. Plaintiff's Responses to DFOF ("Pl. Resp. DFOF") ¶ 167 [Docket No. 409].

Dr. Thakker determined that the C_{min} and C_{max} for the 150 mg tablets are [redacted] µg/ml and [redacted] µg/ml, respectively. Tr. 545:16-19 (Thakker Direct). These values do not satisfy the limitations of Claims 6 and 8 of the '898 and '131 Patents, although they do meet the limitation of Claim 7 of these patents. In fact, Supernus concedes that it does not assert infringement of Claims 6 and 8 of the '898 and '131 Patents by the 150 mg dosage strength of the Actavis Tablets. Pl. Resp. DFOF ¶ 166.

Dosage	**C_{min}**	**C_{max}**	**C_{min}/C_{max}**
600 mg	[redacted] µg/ml	[redacted] µg/ml	[redacted]%
300 mg	[redacted] µg/ml	[redacted] µg/ml	[redacted]%
150 mg	[redacted] µg/ml	[redacted] µg/ml	[redacted]%

The Court is not persuaded by Actavis's argument that the Court should examine the PK Claims in light of the recommended

daily dose of the Actavis ANDA product. The Actavis ANDA labels and prescribing information state that the "[r]ecommended daily dose is 1,200 mg to 2,400 mg once per day." PTX 388.1; PTX 98.4. The Defendants contend that "if the Actavis product is taken as directed, steady state MHD levels" do not fall within the PK Claims. See Defs. Br. at 18-19. The Court finds no merit in this argument. The Patents-in-Suit make no reference to recommended daily doses, let alone those set forth by Actavis. It would be improper to insert these limitations into the Patents-in-Suit.

Furthermore, as the Plaintiff points out, the Actavis label instructs physicians to "[i]nitiate with a dose of 600 mg once per day" in adults and, in children, to "[i]ncrease in weekly increments of 8 mg/kg to 10 mg/kg once daily, not to exceed 600 mg, to achieve target daily dose." PTX 98.4. In geriatric patients, physicians are instructed to begin "at lower dose (300 mg to 450 mg per day) and increase slowly." Id. Clearly, in some circumstances, the recommended daily dose is 600 mg or lower. "It is well settled that an accused device that 'sometimes, but not always, embodies a claim[] nonetheless infringes.'" Broadcom Corp. v. Emulex Corp., 732 F.3d 1325, 1333 (Fed. Cir. 2013) (quoting Bell Commc'n Research, Inc. v. Vitalink Commc'n Corp., 55 F.3d 615, 622-23 (Fed. Cir. 1995)).

For this reason, too, the Court is not persuaded by Actavis's argument.

Given Dr. Thakker's findings, the Court finds that the Actavis 150 mg tablets do not infringe Claims 6 and 8 of the '898 and '131 Patents and that the Actavis 300 mg tablets do not infringe Claim 8 of the '898 and '131 Patents. The Court, however, holds that all three dosage sizes infringe Claim 7 of the '898 and '131 Patents. The 300 mg and 600 mg tablets infringe Claim 6 of the '898 and '131 Patents. Finally, the 600 mg tablets infringe Claim 8 of the '898 and '131 Patents.

(2) Claim 11 of the '898 and '131 Patents

Claim 11 of the '898 Patent discloses "[t]he formulation of claim 10 in the form of tablets." Claim 10 of the '898 Patent, in turn, reads: "The formulation of claim 1 in the form of pellets, tablets, granules or capsules." Claim 11 of the '131 Patent discloses "[t]he method of claim 10, wherein the formulation is in the form of tablets." Claim 10 of the '131 Patent reads: "The method of claim 1, wherein the formulation is in the form of pellets, tablets, granules or capsules." Claim 10 of each of these patents is dependent upon claim 1.

The Court has already found that the Actavis Tablets infringe Claim 1 of the '898 and '131 Patents. Actavis admits that its ANDA product is a pharmaceutical formulation in the form of tablets. Tr. 597:13-17 (Request for Admission). The

Actavis Tablets, therefore, infringe both Claim 10, although not asserted, and Claim 11 of the '898 and '131 Patents.

(3) Claims 18 and 19 of the '898 and '131 Patents

Claims 18 and 19 of the '898 and '131 Patents are both dependent on Claim 1 of the respective patents, but include an additional limitation. Claim 18 of both patents requires that, in addition to meeting the limitations of Claim 1, "the polymer having pH-dependent solubility dissolves at pH values of more than 5." The limitation in Claim 19 of both patents requires that "the polymer having pH-dependent solubility dissolves at pH values of more than 6."

The polymers having pH-dependent solubility in the Actavis Tablets are [redacted] and [redacted]. [redacted] dissolves above pH 5.5, thereby satisfying the limitations of Claim 18 of the '898 and '131 Patents. Tr. 663:21-23 (Little Direct); PTX 50.33. [redacted] is soluble at pH levels above 6.0. Tr. 663:24-1; PTX 50.33. This satisfies Claim 19 of both patents. Therefore, Actavis's ANDA product infringes Claims 18 and 19 of the '898 and '131 Patents.

(4) Claim 21 of the '131 Patent

Claim 21 of the '131 Patent reads: "The method of claim 1, wherein the formulation is administered once a day." The parties agree that Actavis's ANDA product is a pharmaceutical

formulation for the treatment of seizures administered once a day. SF p. 11 ¶ 21. Having already found that the Actavis Tablets infringe Claim 1 of the '131 Patent, the Court further holds that the Actavis Tablets also infringe Claim 21 of the '131 Patent.

2. The '600 Patent

The Plaintiffs assert Claims 1, 7 to 9, 12, 18, and 19 of the '600 Patent. The only independent claim in the '600 patent is Claim 1. Each of the remaining asserted claims depends, directly or indirectly, from Claim 1. Claim 1 of the '600 Patent is largely similar to Claim 1 of the '898 Patent. There are, however, critical differences. Claim 1 of the '600 Patent requires a "solid oral pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix," which in turns comprises:

> (a) oxcarbazepine;
>
> (b) 1-50%, by weight of the formulation, a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
>
> (c) 1-80%, by weight of the formulation, at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
>
> (d) 10-90%, by weight of the formulation, at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group

> consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L 100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers,
>
> wherein, in vitro:
>
> (i) between 20 and 74% of the total oxcarbazepine is released by 2 hours; and
> (ii) between 44 and 96% of the total oxcarbazepine is released by 4 hours.

Actavis's ANDA product is admittedly a "solid oral" tablet for once-a-day administration of oxcarbazepine. SF pp. 11-12 ¶¶ 21, 31-32. The Court has held that the Actavis Tablets additionally comprise a homogeneous matrix comprising oxcarbazepine, a matrix-forming polymer as provided in element 1(b), an agent that enhances the solubility of oxcarbazepine as provided in element 1(c), and at least one release promoting agent as provided in element 1(d).

The question the Court now faces is whether the percent weight limitations found in the '600 Patent are infringed. In resolving this question, the Court relies largely on the figures reported by Actavis to the FDA in its Quality Overall Summary regarding the composition of its 150 mg, 300 mg, and 600 mg tablets, reproduced again below. Actavis does not dispute that

its ANDA product meets element 1(b) of the '600 Patent. SF p. 13 ¶ 38.

Composition of Oxcarbazepine Extended-release Tablets, 150 mg, 300 mg and 600 mg

[redacted]

PTX 116.6

a) Agent that Enhances the Solubility of Oxcarbazepine

This Court has already found that [redacted], present in the Actavis Tablets, acts as an agent that enhances the solubility of oxcarbazepine as required in element 1(c). More importantly, for purposes of this analysis, this Court has held that there is insufficient evidence in the record to support Supernus's position that [redacted] enhances the solubility of oxcarbazepine specifically. [redacted] is found at less than [redacted]% by weight of the formulation in each of the Actavis Tablets. PTX 116.6. [redacted] alone does not satisfy

element 1(c) of the '600 Patent, which requires 1-80%, by weight of the formulation, of an agent that enhances the solubility of oxcarbazepine. Tr. 694:2-12 (Little Cross). Therefore, having found that the only element 1(c) solubilizing agent in the Actavis Tablets is [redacted], the Court holds that the Actavis Tablets do not infringe element 1(c) of the '600 Patent.

b) Release Promoting Agent

The parties agree that [redacted] and [redacted] are both release promoting agents as required by element 1(d) of each of the Patents-in-Suit. [redacted] and [redacted] are also both polymers having pH-dependent solubility. Together the [redacted] make up [redacted]% by weight of the formulation of the Actavis 150 mg tablet, [redacted]% of the 300 mg tablet, and [redacted]% of the 600 mg tablet. PTX 116.6; Tr. 660:6-18 (Little Direct). These two excipients alone do not satisfy element 1(d) of the '600 Patent, which requires the release promoting agent to be present in an amount from 10% to 90% by weight of the formulation. Tr. 679:2-10 (Little Cross).

Supernus argues, however, that [redacted], found in the Actavis Tablets in the form of [redacted], also acts as an element 1(d) release promoting agent in the Actavis Tablets, despite the fact that it is not a polymer and does not have pH-dependent solubility. See, e.g., Tr. 660:19-661:11 (Little Direct); Tr. 679:11-17

(Little Cross); Tr. 1380:20-24 (Hopfenberg Direct). In support of this position, Supernus directs the Court to the specifications of the Patents-in-Suit which state that "[t]he release promoters are not limited to pH dependent polymers. Other hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can also be used for the same purpose." '600 Patent, col. 5, ll. 2-6. Therefore, in Supernus's view, the proper reading of element 1(d) does not require all release promoting agents to be polymers with pH-dependent solubility.

Dr. Little testified that [redacted] is "a hydrophilic molecule that people use to put into a formulation and it will dissolve away leaving a pore," in the manner described in the specification. Tr. 660:25-661:11 (Little Direct). By weight of the formulation, it makes up [redacted]%, [redacted]%, and [redacted]% of the Actavis 150 mg, 300 mg, and 600 mg tablets, respectively. PTX 116.6. [redacted], combined with the [redacted], is present in an amount over 10% by weight of the formulation in each of the Actavis Tablets. The Court must evaluate, however, the propriety of including [redacted] in this analysis.

The parties dispute the scope of the claim language, particularly the word "comprising." Claim element 1(d) of the '600 Patent requires "10-90%, by weight of the formulation, at

least one release promoting agent comprising a polymer having pH-dependent solubility selected from" a group of polymers. On the one hand, Actavis argues that only polymers with pH-dependent solubility may satisfy this element. Defs. Br. at 17-18. Supernus, on the other hand, contends that molecules that act as release promoters, even if they are not polymers with pH-dependent solubility, may meet this limitation because the word "comprising" is "an open-ended term of art in patent law that does not exclude additional, unrecited elements." Plaintiff's Post-Trial Brief ("Pl. Br.") at 25 [Docket No. 394].

Dr. Little testified that when he reads element 1(d) of each of the Patents-in-Suit, he first "[breaks] it down into several pieces[.]" Tr. 658:14-17 (Little Direct). Under his reading, "[t]he requirement [in element 1(d) of the '600 Patent] would be the formulation must contain 10 to 90 percent by weight of one or more release promoting agents of any type." Id. at 658:22-24. He then continued: "Following at least one release promoting agent is comprising a polymer having pH-dependent solubility. So, my read on that is that at least one release promoting agent must include at least one polymer having pH-dependent solubility but may include other release promoters." Id. at 658:25-659:4. This is a construction that Dr. Little formulated along with counsel for Supernus. Tr. 676:19-678:5 (Little Cross).

While the Court is skeptical of Supernus's reading of the claim language, and is hampered by having no claim construction hearing on this term, it need not resolve this issue because, regardless of the scope of the claim language, Supernus has not carried its burden of proving by a preponderance of the evidence that [redacted] acts a release promoting agent in the Actavis Tablets. Assuming that the Plaintiff is correct that element 1(d) encompasses "[o]ther hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure," '898 Patent, col. 4, ll. 64-67, the Court holds that Supernus has not established by a preponderance of the evidence that [redacted] is such a molecule.

Supernus relies almost exclusively upon the testimony of Dr. Little to establish that [redacted] acts as an element 1(d) release promoting agent. Dr. Little testified that "[redacted] is a hydrophilic molecule that people use to put into a formulation and it will dissolve away leaving a pore. . . . it's actually a very similar mechanism that's discussed in the specification for how the release promoter functions, by dissolving and leaving pores that would then work together with the other pieces of the (a) through (d) in order to produce an enhanced formulation." Tr. 661:2-11 (Little Direct). He did not elaborate on his experience or familiarity with [redacted] or its release promoting properties.

Additionally, he did not explain who the "people" who use [redacted] in their formulations are. Aside from this testimony, there is a dearth of other evidence in the record supporting the Plaintiff's position that [redacted] acts as a release promoter, as contemplated by the patent specifications, in the Actavis Tablets.

On cross-examination, Dr. Little confirmed that, assuming all the other limitations were met, "a formulation [with] a trivial amount of pH-dependent polymer and ten percent [redacted] would infringe the '600 Patent. See Tr. 680:16-681:17 (Little Cross). Yet, in spite of its potentially central role, the evidence regarding [redacted] is sparse. Notably, the record is devoid of any references of testing or experimentation conducted by Dr. Little or any others involved in this litigation regarding the release promoting characteristics of [redacted] generally or in the Actavis Tablets.

Dr. Hopfenberg likewise testified that his "experience is limited to the fact that [redacted] is not a polymer and it dissolves rapidly." Tr. 1456:5-8 (Hopfenberg Cross). He continued: "I never witnessed a formulation where it [redacted] leaches out [of] the dosage form quickly leaving a porous structure that can be used for the same purpose. I have no experience with that specific experiment." Id. at 1456:8-12.

His lack of familiarity with [redacted] properties only serves to highlight the Court's concerns.

The Court finds that the limited evidence put forth by the Plaintiff regarding [redacted] is insufficient to carry its burden of proof as to element 1(d) of the '600 Patent.

Therefore, for the reasons set forth above, the Court holds that that the Actavis Tablets do not infringe Claim 1 of the '600 Patent, as Supernus has failed to meet its burden of proving infringement as to claim element 1(c) and 1(d). Having found no infringement of independent Claim 1 of the '600 Patent, the Court need not address the remaining dependent claims. Ferring B.V. v. Watson Labs., Inc.-Florida, 764 F.3d 1401, 1411 (Fed. Cir. 2014); Monsanto, 503 F.3d at 1359 ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim."). There is, therefore, no infringement of the '600 Patent by any of the Actavis Tablets.

C. Invalidity

A patent and each of its claims are presumed to be valid, even where those claims may be dependent upon other invalid claims in the patent. 35 U.S.C. § 282(a). A party may rebut this presumption of validity with clear and convincing evidence of invalidity. Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253, 1260 (Fed. Cir. 2012) (citing 35 U.S.C. § 282 and Microsoft

Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2245 (2011)). To be clear, the burden of establishing invalidity by clear and convincing evidence remains on the party asserting invalidity. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1078 (Fed. Cir. 2012). "The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and a 'preponderance of the evidence' . . . [and] has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" Buildex Inc. v. Kason Indus., Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

Where an invalidity challenge is based upon prior art that was considered by the PTO during the patent prosecution, and where a patent was issued notwithstanding the prior art, "a court owes some deference to the PTO's decision." Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1572 (Fed. Cir. 1992) (citations omitted). Although a defendant's burden does not change, evidence considered by the PTO may not be given the same weight as new evidence. See Sciele Pharma, 684 F.3d at 1260 ("[N]ew evidence not considered by the PTO 'may carry more weight . . . than evidence previously considered by the PTO,' and may 'go further toward sustaining

the attacker's unchanging burden.'") (quoting Microsoft Corp., 131 S. Ct. at 2251).

As a defense to infringement, the Defendants assert the following grounds for invalidity: obviousness, lack of written description, and indefiniteness.

1. Obviousness

A patent is invalid as obvious if the differences between the claimed invention and the prior art are such that the invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. Sciele Pharma, 684 F.3d at 1259 (quoting 35 U.S.C. § 103(a)). Whether a patent claim is obvious is a question of law based on four underlying facts: (1) the scope and content of the prior art; (2) the differences between the prior art and the claim at issue; (3) the level of ordinary skill in the pertinent art; and (4) such secondary considerations as commercial success, long-felt but unmet need, and the failure of others. Id. (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)); see also KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 406 (2007).

Generally, this inquiry considers whether a person skilled in the art would have had (1) reason to combine the teachings of the prior art references to achieve the claim invention, and (2) a reasonable expectation of success in doing so. In re Cyclobenzaprine, 676 F.3d at 1068-69 (internal citations

omitted). "[O]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988); see also Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1350 (Fed. Cir. 2009); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In KSR, the Supreme Court cautioned that this inquiry must be "expansive and flexible" and must account for the fact that a person of ordinary skill in the art is also "a person of ordinary creativity, not an automaton." 550 U.S. at 415, 421. There need not be "precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id. at 418.

Importantly, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Id. at 417. Relevant to this analysis is whether there was a reason or motivation to combine the known elements in the manner claimed by the patent. Id. at 418. Indeed, "[o]ne of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at

the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." Id. at 419-20. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. at 420.

Finally, an invention is "obvious-to-try" and therefore invalid under 35 U.S.C. § 103 if it results from a skilled artisan merely pursuing "known options" from "a finite number of identified, predictable solutions." In re Cyclobenzaprine, 676 F.3d at 1070 (quoting KSR, 550 U.S. at 421) (internal quotations omitted). It is crucial to keep in mind, however, that "knowledge of [a] a goal does not render its achievement obvious." Abbott Labs. V. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008).

The Defendants contend that the asserted claims are obvious in light of a combination of prior art references setting forth oxcarbazepine and extended-release carbamazepine formulations for the treatment of seizures. The Court will address each of the prior art references in turn.

The Court will first address the scope and content of the prior art, as well as the differences between the claimed invention and the prior art. Next, the Court will assess whether a skilled artisan would have been motivated to combine the teachings of the prior art to formulate oxcarbazepine once

daily, and whether such a person would have had a reasonable expectation of success in doing so. Finally, the Court will evaluate the objective indicia of non-obviousness, or secondary considerations, and then set forth its conclusions of law.

a) Scope and Content of the Prior Art and Differences between the Prior Art and the Claimed Invention

By 2006, as described above, several drugs for the treatment of seizures were available on the market, including immediate release oxcarbazepine formulations and both immediate and extended release carbamazepine formulations. While immediate release oxcarbazepine has been available since 2000 and other AEDs have been reformulated as extended release, once daily products, no effective once daily oxcarbazepine formulation was developed prior to 2006.

At the time of Supernus's invention, it was well known that significant and material differences exist between carbamazepine and oxcarbazepine. See, e.g., PTX 327.18; PTX 341; Tr. 1700:11-1710:25 (Thakker Direct). The peer-reviewed literature and prior art also established that obstacles exist to creating an effective once daily oxcarbazepine formulation. See, e.g., PTX 230.3; DTX 199 at ACT-OXXR002756316.

Notwithstanding these impediments, the Defendants argue that, in light of a combination of prior art references, Supernus's once daily formulation of oxcarbazepine to treat

seizures was obvious. The Defendants rely upon several prior art references disclosing AED formulations, including one oxcarbazepine formulation and several carbamazepine formulations, as well as a prior art reference disclosing extended release antimicrobial agents.

(1) The Franke Patent

The only oxcarbazepine formulation the Defendants identify in the prior art is International Publication No. WO 03/101430 (the "Franke Patent"). DTX 199. Actavis argues, through Dr. Mayersohn, that the Franke Patent "show[ed] that one can create a once-a-day form of oxcarbazepine." Tr. 1132:2-3 (Mayersohn Cross); see also Tr. 1090:18-1092:7 (Mayersohn Direct).

The Patent Examiner, however, considered the Franke Patent during the prosecution of the Patents-in-Suit and found that Supernus's invention was not covered by the prior art. See PTX 5.219-20; PTX 1.2; PTX 2.2; PTX 3.2; Tr. 1138:7-8 (Mayersohn Cross). Actavis, therefore, has "the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." Shire LLC v. Amneal Pharm., LLC, 802 F.3d

1301, 1307 (Fed. Cir. 2015). The Court finds that Actavis has not met this burden.

According to Dr. Mayersohn, the blood level concentration profile disclosed in the Franke Patent after a single dose would "allow a person of ordinary skill to reach a reasonable conclusion that that would provide once-a-day therapy if multiple dosed." Tr. 1139:13-16, 1145:9-15 (Mayersohn Cross). Apydan® Extent, the only commercial embodiment of the Franke Patent, however, is a twice daily formulation. Id. 1133:20-1134:2. In fact, the specifications of the Patents-in-Suit distinguish the present invention from the Franke Patent, observing that "the solubility and bioavailability of the drug from [the Franke Patent] [was not] suitable for once-a-day administration." '898 Patent, col. 2, ll. 12-14.

Dr. Mayersohn went so far as to testify that "from a lot of the patents that [he has] reviewed," he believes that nearly any invention for once daily administration is obvious if it has previously been formulated for twice daily administration. Tr. 1148:2-8, 1151:6-14 (Mayersohn Cross). As Supernus correctly points out, "[a]lmost any invention, no matter how nonobvious at the time, will appear obvious when looking backward from the solution." Pl. Br. at 30 (citing Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc., 456 F. Supp. 2d 644, 662 (D.N.J. 2006)). The Court does not credit this "hindsight reconstruction" in its

obviousness analysis. See Janssen, 456 F. Supp. 2d at 662. Likewise, the fact that a goal is known "does not render its achievement obvious." Abbott Labs., 544 F.3d at 1352.

The Court is instead persuaded by Supernus that the Franke Patent discloses immediate-release twice-a-day oxcarbazepine formulations and teaches away from once daily administration of oxcarbazepine. The Franke Patent teaches ***in vitro*** release profiles wherein 90-100% of the oxcarbazepine is released in sixty minutes, indicating an immediate release profile. DTX 199 at ACT-OXXR002756316-17; Tr. 1653:7-18 (Little Direct). Dr. Little testified that the Franke Patent "is an immediate-release product." Id. at 1653:14. In fact, the Franke Patent itself states: "The result is surprising because the in vitro release curve of oxcarbazepine of the compositions according to this invention is only slightly below that of the commercial [immediate-release, twice daily] tablets in which no adequate prolongation of the effect is normally expected." DTX 199 at ACT-OXXR002756316. Dr. Hopfenberg agreed that the ***in vitro*** release profile in the Franke Patent "would not have been viewed by a person of ordinary skill in the art as likely to provide 24 hours of therapy." Tr. 1497:10-1499:1 (Hopfenberg Cross). What's more, the Franke Patent explicitly observes that oxcarbazepine formulations with controlled release profiles, such as those that release approximately 40% of the

oxcarbazepine within 60 minutes "turned out to be ineffective." DTX 199 at ACT-OXXR002756316.

Furthermore, the Franke Patent does not teach the use of element 1(c) agents that enhance the solubility of oxcarbazepine. Tr. 1654:14-20 (Little Direct).

(2) The Carbamazepine Prior Art

The Katzhendler and two Rudnic Patents (as defined below) relied upon by the Defendants are directed to carbamazepine formulations. Dr. Hopfenberg testified that if a person skilled in the art were attempting to develop an extended release oxcarbazepine formulation, the person would look to prior art involving other materials that are similar to oxcarbazepine in terms of use, solubility, and molecular structure, such as carbamazepine. Tr. 1409:617 (Hopfenberg Direct). Dr. Hopfenberg premised his obviousness opinions on the similarities between oxcarbazepine and carbamazepine, essentially treating them as interchangeable. See Tr. 1445:4-13 (Hopfenberg Cross). Dr. Hopfenberg testified that his understanding is that "Carbamazepine, oxcarbazepine are identical except for the carbonyl group." Id. at 1451:6-8.

The presence of a carbonyl group in oxcarbazepine, however, is a critical difference that impacts how the molecule interacts with water. See id. at 1448:3-5. In addition to this, the literature establishes many other significant differences

between oxcarbazepine and carbamazepine that undermine the Defendants' obviousness argument. The 2003 article by Theodor May et al. entitled Clinical Pharmacokinetics of Oxcarbazepine, explained that although oxcarbazepine and carbamazepine have similar chemical structures, "significant differences exist in pharmacokinetics and drug interactions between these two drugs." PTX 327.18. The authors caution that oxcarbazepine and carbamazepine "should be considered as distinct therapeutic agents." Id. Another article published in 2004 by Dieter Schmidt and Christian E. Elger, entitled What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs?, described the differences between oxcarbazepine and carbamazepine as including differences in "mode of action and metabolism, but also, in particular, in terms of the proven efficacy and good tolerability of [oxcarbazepine]." PTX 341.7.

Moreover, Dr. Thakker testified as to the differences between how the body absorbs, distributes, metabolizes, and excretes oxcarbazepine and carbamazepine. See Tr. 1700:11-1710:25 (Thakker Direct) ("[T]he two compounds . . . certainly [once] th[ey] get into the body are processed by the body with respect to all four processes, absorption, it's distribution, it's metabolism and it's elimination . . . the body really treats them as very, very different compounds."). Dr. Thakker

identified, for example, the vastly different half-lives of the two compounds. While carbamazepine has a half-life between twenty-five and eighty-five hours, oxcarbazepine's half-life is roughly two hours. Id. at 1709:20-1710:12, 1710:20-25.

Dr. Hopfenberg, on the other hand, did not consider the chemical, pharmacokinetic, and other differences between carbamazepine and oxcarbazepine. See Tr. 1445:19-1447:19, 1448:18-22, 1451:9-11 (Hopfenberg Cross). Given that Dr. Hopfenberg's obviousness analysis is premised on the false assumption that oxcarbazepine is interchangeable with carbamazepine, the Court finds that Actavis has not met its burden of demonstrating the prior art directed to carbamazepine renders the Patents-in-Suit obvious. Nonetheless, the Court will address in more detail the Katzhendler and Rudnic Patents.

The Katzhendler Patent

U.S. Patent No. 6,296,873 (the "Katzhendler Patent") teaches sustained release formulations of carbamazepine and certain carbamazepine derivatives. DTX 114. As with the Franke Patent, the PTO considered the Katzhendler Patent during prosecution of the Patents-in-Suit and issued the Supernus Patents notwithstanding.

Actavis posits that since the Katzhendler Patent specification lists oxcarbazepine first on a list of carbamazepine derivatives, the teachings of this patent are

directed to extended release oxcarbazepine formulations. Tr. 1404:4-13 (Hopfenberg Direct). Supernus correctly emphasizes, though, that aside from this list, the Katzhendler Patent "does not otherwise mention oxcarbazepine or provide any direction to select oxcarbazepine for a once-a-day product." Pl. Br. at 35.

As outlined above, however, there are noteworthy and numerous differences between carbamazepine and oxcarbazepine. The Katzhendler Patent itself also indicates that the two compounds are not interchangeable. The Katzhendler Patent specification explains that the "preferred" release accelerating agent is polyethylene glycol. DTX 114 at col. 10, ll. 28-30. Oxcarbazepine, though, is not compatible with polyethylene glycol, demonstrating that oxcarbazepine and carbamazepine are not simply interchangeable. See, e.g., PTX 356.24; Tr. 1660:21-1661:3, 1663:6-19 (Little Direct) (testifying that excipient compatibility studies show that polyethylene glycol degrades oxcarbazepine); Tr. 72:11-74:10 (Bhatt Direct).

Moreover, the Katzhendler Patent teaches away from the use of release promoting polymers with pH-dependent solubility, which are required in element 1(d) of the Patents-in-Suit. The Katzhendler Patent, instead, calls for polymers that inhibit release and "slow[] down the water penetration into the tablet and thus slow[] the tablet erosion." DTX 114 at col. 9, ll. 45-62. Additionally, the Katzhendler Patent is directed to

pharmaceutical formulations with zero-order release profiles, meaning linear or straight release profiles. Tr. 1661:8-1663:19 (Little Direct). Polymers with pH-dependent solubility are necessarily inconsistent with zero-order release profiles and, therefore, with the Katzhendler Patent's teachings. Id. Such a modification would be improper. See Plas-Pak Indus., Inc. v. Sulzer Mixpac AG, 600 F. App'x 755, 758 (Fed. Cir. 2015) ("[C]ombinations that change the basic principles under which the prior art was designed to operate, or that render the prior art inoperable for its intended purpose, may fail to support a conclusion of obviousness.") (internal quotations, citations, and modifications omitted).

The Rudnic Patents

Actavis likewise relies on U.S. Patent No. 5,325,570 (the "Rudnic '570 Patent") and U.S. Patent No. 5,912,013 (the "Rudnic '013 Patent and, collectively, the "Rudnic Patents"). DTX 113; DTX 344. The Rudnic Patents are also directed to carbamazepine formulations and contain no teachings regarding oxcarbazepine. Tr. 1495:9-20 (Hopfenberg Cross). The carbamazepine formulations disclosed in the Rudnic Patents are multiple unit, or pellet, dosage forms for administration "preferably twice a day." DTX 113 at col. 1, ll. 44-45, col. 2, ll. 62-64. Carbatrol®, a commercial embodiment of the Rudnic Patents, is

administered twice daily. Tr. 1487:24-1488:14 (Hopfenberg Cross).

In addition to having a different dosing frequency and active ingredient than the Patents-in-Suit, the Rudnic Patents also teach away from a homogeneous matrix tablet. The formulations in the Rudnic Patent require "three different units in order for [them] to work." Tr. 1664:8-25 (Little Direct). Rather than having all the constituents uniformly dispersed across a matrix tablet, the formulations disclosed in the Rudnic Patents include separate pellets in each dose. Multi-pellet formulations are not homogeneous matrix formulations. Id.

Dr. Hopfenberg opined that a person of ordinary skill in the art would rely on the formulation of Pellet C described in the Rudnic '570 Patent, in combination with other prior art references, to arrive at a once daily oxcarbazepine homogeneous matrix tablet. Tr. 1415:9-1420:10 (Hopfenberg Direct); Tr. 1495:25-1496:4 (Hopfenberg Cross). The dissolution profile of Pellet C is also vastly different from that disclosed in the Supernus Patents. DTX 113 at Fig. 1; Tr. 1496:15-21 (Hopfenberg Cross).

The Court agrees with the Plaintiff that the Defendants have "failed to explain how or why a formulator would select one of the dozens of **carbamazepine** pellets disclosed in Rudnic and modify that particular pellet to arrive at Supernus's claimed

oxcarbazepine formulations." Pl. Br. at 37 (emphasis in original). Additionally, Dr. Hopfenberg could recall no examples teaching that Pellet C alone could be efficaciously administered. Tr. 1497:4-9 (Hopfenberg Cross).

The Oren Patent

Finally, the Defendants rely upon European Patent Publication No. 0 280 571 (the "Oren Patent") as prior art. DTX 390. The Oren Patent discloses sustained release matrix formulations of antimicrobial agents. DTX 390 at p. 2. It is unrelated to oxcarbazepine, carbamazepine, or any other anti-epileptic drug. Tr. 1499:12-13 (Hopfenberg Cross). The Oren Patent does not disclose a homogeneous matrix. Id. at 1491:9-14. The Court agrees with Dr. Little that there is no reason for a person of ordinary skill in the art to consult the Oren Patent in attempting to formulate a once daily oxcarbazepine formulation comprising a homogeneous matrix. See Tr. 1665:11-14 (Little Direct).

b) Motivation to Combine Prior Art References to Formulate Once-Daily Oxcarbazepine Treatment for Seizures & Reasonable Expectation of Success

The Defendants put forth evidence to demonstrate that a person skilled in the art would have been motivated to develop an extended-release oxcarbazepine drug for the treatment of seizures. For example, Dr. Mayersohn testified regarding the

commercial motivation to develop an extended-release oxcarbazepine drug based on the development of extended-release formulations of other drugs used to treat seizures. Tr. 1077:1-20 (Mayersohn Direct). Carbamazepine and divalproex entered the market as immediate-release anti-epileptic drugs in the 1960s. Extended-release formulations of carbamazepine entered the market under the brand names Tegretol XR® and Carbatrol® in the 1990s. An extended-release formulation of divalproex has been available since 2000, marketed under the name Depakote ER®. Id. at 1077:7-14. Immediate-release oxcarbazepine in the form of Trileptal® has been available and known to treat seizures since 2000. Dr. Mayersohn testified that, based on the progression of other anti-epileptic drugs, a person of ordinary skill in the art would have clearly been motivated to make an extended-release formulation of oxcarbazepine and that the prior art predicted the ability to do so. Id. at 1077:15-20.

Actavis's position, however, disregards the prior art and literature suggesting that oxcarbazepine is not suitable for an extended release formulation. The mere fact that a goal is known and desired does not lead to the conclusion that its achievement is obvious. Abbott Labs., 544 F.3d at 1352. And yet, in coming to his obviousness opinion, Dr. Mayersohn did not examine any scientific impediments to making a once daily

oxcarbazepine formulation because it was "not important" to his analysis. Tr. 1126:10-19 (Mayersohn Cross).

On the contrary, such impediments are critical to the question of whether a person of ordinary skill in the art would be motivated to combine certain prior art references. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 550 U.S. at 418. "[T]he law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention." Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1361 (Fed. Cir. 2011).

In this Court's opinion, Supernus's concession that "[t]he need for a controlled-release dosage form for drugs taken chronically such as oxcarbazepine and derivatives is self-evident," '898 Patent, col. 1, ll. 33-35, is more probative of long-felt need than obviousness or the motivation of a person skilled in the art to combine the prior art references to develop a once daily extended release oxcarbazepine formulation. While Dr. James Wheless testified that "[t]he next obvious kind of thought" was to make an extended release oxcarbazepine formulation, Tr. 1190:18-20 (Wheless Direct), this says little about motivation of a person of ordinary skill in the art to

combine the teachings of the prior art that the Defendants have identified to create this desired formulation.

Contrary to Actavis's position, Supernus did "show that oxcarbazepine had [certain] peculiar characteristics known in the prior art that would 'demotivate' the POSA from starting down the path toward developing a once-daily formulation." Defs. Br. at 22. For example, the 2000 Collins and Garnett article, entitled Extended Release Formulations of Anticonvulsant Medications: Clinical Pharmacokinetics and Therapeutic Advantages, explained that "oxcarbazepine would not be an appropriate candidate [for extended release development] because it is essentially a prodrug and is rapidly and extensively metabolized to its primary active metabolite.[23] It is recommended that oxcarbazepine is administered twice daily." PTX 230.3; Tr. 1694:11-15 (Thakker Direct). Dr. Thakker testified that, given the fact that oxcarbazepine is "essentially a prodrug," a person skilled in the art would not be motivated to formulate a once daily oxcarbazepine

[23] When asked to describe a prodrug, Dr. Thakker explained: "So, we know that oxcarbazepine, even during its absorption, it extensively gets metabolized in the liver and it produces the hydroxyl, monohydroxy which we call MHD, and the majority of the pharmacological activity of oxcarbazepine is really attributed to the MHD. So, whenever you have a drug that you administer and it produces another chemical entity as a result of metabolism, which is then the pharmacological entity, we generally refer to that as a prodrug." Tr. 1693:1-11 (Thakker Direct).

formulation, despite the theoretical desirability of such a product. Tr. 1694:23-1695:2 (Thakker Direct). In fact, Oxtellar XR® "is the only epilepsy medication we have that's ever been a prodrug that's been able to be made into an extended-release product." Tr. 1216:8-13 (Wheless Direct).

Additionally, oxcarbazepine exhibited an "absorption window," which resulted in bioavailability obstacles for formulators attempting to create an extended-release once daily oxcarbazepine AED. Tr. 1697:18-23 (Thakker Direct). Due to the absorption window, oxcarbazepine's bioavailability and effectiveness decreases when it is released outside of this absorption window. See PTX 224.1; Tr. 56:4-20, 57:23-60:13 (Bhatt Direct). Oxcarbazepine's absorption window was observed not only by the Jazz formulators, see, e.g., PTX 224.1; Tr. 56:14-20 (Bhatt Direct), but it was also encountered in the Franke Patent. See Tr. 1697:18-1700:1 (Thakker Direct). The Franke Patent states that "Typical controlled-release formulas with a low subsequent ***in-vitro*** release profile (60 min: about 40% oxcarbazepine release) however turned out to be ineffective." DTX 199 at ACT-OXXR00275316. Dr. Thakker credibly testified that the controlled-release formulas that the Franke Patent inventors found to be ineffective suffered from "performance [that] was poor in terms of absorption of the

active ingredient" as a result of oxcarbazepine's absorption window. Tr. 1699:19-1700:1 (Thakker Direct).

Moreover, Dr. Thakker testified that significant experimentation would be required to identify the specific absorption window of oxcarbazepine, as the specific contours of the obstacle were not identified or overcome in the prior art. See Tr. 1716:16-1718:10 (Thakker Cross). "Without the knowledge of a problem, one of skill in the art would not have been motivated to modify" the prior art to solve the problem. Novartis Pharm. Corp. v. Watson Labs., Inc., 611 F. App'x 988, 996 (Fed. Cir. 2015).

Defendants rely upon Allergan, Inc. v. Watson Labs., Inc. – Florida, 869 F. Supp. 2d 456, 483 (D. Del.) aff'd, 470 F. App'x 903 (Fed. Cir. 2012) to demonstrate that an absorption window impediment is no impediment at all. However, in Allergan, the district court explained that "persons of skill in the art had numerous references available that addressed trospium's positive attributes as well as how to remedy trospium's negative attributes." Id. Here, no prior art has been identified that details "how to remedy [oxcarbazepine's] negative attributes."

Finally, Supernus is correct that the evidence "includes reports of unequivocal failures by skilled formulators trying to develop a once-a-day oxcarbazepine product." Pl. Br. at 30. For instance, Dr. Bhatt testified that the Jazz Pharmaceuticals

and Shire joint venture was terminated when the formulators were unsuccessful in developing an effective once-a-day oxcarbazepine formulation. See, e.g., Tr. 57:23-60:13 (Bhatt Direct). Likewise, Actavis developed over one hundred different experimental formulations in its attempt to develop a generic once daily oxcarbazepine drug before it developed the accused product. See, e.g., Tr. 1642:1-7, 1643:14-1651:8 (Little Direct); PTX 72.12-14, 26-28. "While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure." In re Cyclobenzaprine, 676 F.3d at 1081 (quoting Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir. 2003)).

c) Secondary Considerations

As the Court concludes that Actavis has failed to meet its burden of proving obviousness, the Court need not address the objective indicia of non-obviousness, or secondary considerations. Nonetheless, it will do so.

"[S]econdary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented" and "may have relevancy" as indicia as obviousness or non-obviousness. Graham, 383 U.S. at 17-18. "A nonmovant may rebut a prima facie

showing of obviousness with objective indicia of nonobviousness." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) (citing WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999); In re Kahn, 441 F.3d 977, 990 (Fed. Cir. 2005)).

(1) Long Felt But Unmet Need

Dr. Wheless testified as to the secondary considerations supporting non-obviousness. Dr. Wheless is the former Chief of Pediatric Neurology at St. Jude's Children's Hospital and current Chief of Pediatric Neurology at the University of Tennessee Health Science Center and Director of Le Bonheur Neuroscience Institute and Comprehensive Epilepsy Program. PTX 524. He has treated over one hundred patients with Oxtellar XR® since its commercial release. Tr. 1183:17-21 (Wheless Direct). He has also converted patients from Trileptal®, the twice daily oxcarbazepine formulation, to Oxtellar XR® and has observed better tolerance for increased dosages in many of those patients. Id. at 1187:10-20. Some of his patients who continued to have seizures while taking Trileptal® finally achieved seizure freedom after taking Oxtellar XR®. Id. at 1187:17-20. Dr. Wheless has never switched a patient from Oxtellar XR® to Trileptal®. Id. at 1187:21-23.

In Dr. Wheless's opinion, as an expert in neurology and the treatment of epilepsy, Oxtellar XR® satisfied a long felt but

previously unmet need for an extended release, once daily oxcarbazepine formulation for the treatment of seizures. See, e.g., id. at 1189:2-5. Oxcarbazepine was first released in an immediate-release formulation in 2000. While this in itself was an improvement over other anti-epileptic drugs, such as carbamazepine, Dr. Wheless explained, there was still a need to reduce side effects, improve tolerability, and increase patient adherence and compliance. Id. at 1190:18-24.

According to Dr. Wheless, Oxtellar XR® satisfied these needs. Patients taking Oxtellar XR® report fewer side effects than those taking carbamazepine or twice daily oxcarbazepine. Id. 1191:5-12. Dr. Wheless's patients also displayed improved tolerability on Oxtellar XR® as opposed to immediate release oxcarbazepine. Id. at 1192:5-14. The results of Supernus's Phase III clinical trials for Oxtellar XR® also support this conclusion. PTX 388.8-12. The results indicated that the incidence for any given side effect was roughly fifty percent lower for patients on Oxtellar XR® as compared to those on immediate release oxcarbazepine. Tr. 1193:18-24 (Wheless Direct); PTX 388.9-11. Dr. Wheless testified that it is rare, if not unheard of, for the FDA to include such comparisons in product labels. Tr. 1194:13-19 (Wheless Direct). While the FDA's inclusion of this comparison in the Oxtellar XR® label is "unique," id., this information is useful because, "as a

practitioner, it's helpful to see the side-by-side side effect profile when I think about prescribing this product to realize there are two distinctly different products, that one has a better side effect profile." Id. at 1195:20-25.[24]

Patients taking Oxtellar XR® also demonstrated improved adherence. Dr. Wheless attributed this in part to the reduced incidence of side effects, which causes fewer disruptions in patients' lives. With fewer side effects, patients are more likely to be diligent about taking their medication even before important meetings or school, for example. Id. at 1199:11-21. Given the high stakes involved, improving patient compliance is of critical importance. Id. at 1201:7-19.

The Court, however, appreciates the Defendants' point that "[t]here is still, today, an ongoing need for more and better AEDs." DFOF ¶ 401 (citing Tr. 1249:17-24 (Lado Direct)). Certainly, Oxtellar XR® may not have resolved every long felt need related to the treatment of epilepsy and the Court does not doubt Actavis's view that there continues to be room for further

[24] The Court notes, as did Actavis, that the Oxtellar XR® label also cautions against directly comparing adverse event frequencies because the immediate release oxcarbazepine and Oxtellar XR® were not examined in the same trial. PTX 388.10. While these comparisons should perhaps be viewed with some skepticism, the Court, however, agrees with Dr. Wheless that the comparison is a relevant one, both for prescribing physicians and for the analysis of secondary considerations. See Tr. 1221:16-1222:8 (Wheless Cross).

improvement and development of AEDs. That being said, Supernus has identified a long felt need for an extended release, once daily formulation of oxcarbazepine to treat seizures that results in an improved side effect profile, as well as increased tolerability and patient compliance. The Court further finds that Oxtellar XR® met this need.

(2) Industry Skepticism

"General skepticism of those in the art – not amounting to teaching away – is also 'relevant and persuasive evidence' of nonobviousness." Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (quoting Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 726 (Fed. Cir. 1990)). The Court finds that Supernus has established industry skepticism that an effective once daily oxcarbazepine formulation for the treatment of seizures could be developed.

Dr. Wheless testified that, in light of Dr. Bhatt's testimony and peer-reviewed literature regarding twice daily Apydan® Extent, there was industry skepticism that an effective once daily oxcarbazepine formulation could be developed. Tr. 1212:10-14 (Wheless Direct). While the "reformulation of immediate-release anti-epileptic drugs into extended release formulations has been part of the life-cycle of such drugs," Defs. Br. at 29, there is no certainty that such a goal can be achieved since each active ingredient exhibits different

properties that may impede the development of an extended release version.

The 2007 Meir Bialer article, for example, demonstrated the industry's view that oxcarbazepine did not "fit the model for once daily administration." Id. at 1213:14-18; PTX 555. The Franke Patent similarly counseled that controlled-release oxcarbazepine formulations "turned out to be ineffective." DTX 199 at ACT-OXXR002756316. The 2000 Collins and Garnett article also stated that "Oxcarbazepine would not be an appropriate candidate [for extended release formulation] because it is essentially a prodrug and is rapidly and extensively metabolized to its primary active metabolite. It is recommended that oxcarbazepine is administered twice daily." PTX 230.3. Finally, after its formulators were unable to develop an effective once daily oxcarbazepine formulation, Jazz terminated its joint venture with Shire, demonstrating, in both Dr. Bhatt and the Court's opinions, its skepticism that such an objective could be achieved. See Tr. 64:9-19, 65:25-66:6 (Bhatt Direct).

(3) Failure of Others

Evidence of the failure of others may be "determinative on the issue of obviousness." Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000). There is no dispute that Supernus developed and marketed the first once

daily extended release oxcarbazepine formulation for the treatment of seizures.

Dr. Wheless concluded that, before Supernus succeeded, others had attempted to formulate a once daily oxcarbazepine to treat seizures, but failed. Tr. 1202:19-21 (Wheless Direct). He based his opinion upon his own experience as a neurologist and epileptologist, peer-reviewed literature, and Apydan® Extent, the commercial embodiment of the Franke Patent. Id. at 1202:21-25. For example, Dr. Wheless testified that he had discussions with representatives of Novartis, the pharmaceutical company that developed the immediate release oxcarbazepine formulation known as Trileptal®, regarding extended release formulations. Id. 1204:25-1205:6. To date, Novartis has not marketed an extended release oxcarbazepine formulation. While this may be an interesting observation, this Court does not find that this alone supports the position that Novartis tried and failed to formulate an extended release oxcarbazepine product.

There is, however, evidence that the Franke Patent inventors attempted, but failed to formulate an effective once daily oxcarbazepine product. See, e.g., id. at 1206:19-22; Tr. 1697:25-1700:1 (Thakker Direct). Dr. Wheless, for example, relied upon the Bialer article, which reviewed extended release formulations of anti-epilepsy drugs, including Apydan® Extent, the commercial embodiment of the Franke Patent. Tr. 1206:1-12,

22-25 (Wheless Direct); PTX 555. Apydan® Extent is not approved in the United States, but it was approved in Germany as a twice daily formulation only. Tr. 1206:22-25 (Wheless Direct). The Bialer article describes a phase III clinical trial, in which patients took Apydan® Extent once daily. These patients suffered twice as many seizures as patients taking Trileptal® twice daily. Tr. 1230:19-1231:1 (Wheless Cross).

Jazz and Shire's joint venture to develop an effective once daily oxcarbazepine product also failed after months of experimentation and was eventually terminated due to its failure. See, e.g., Tr. 1634:11-24 (Little Direct); Tr. 57:23-60:13 (Bhatt Direct). While the Court considers this in its analysis, it is not determinative. The Defendants aptly note that "Jazz may have paid the bills, but Drs. Bhatt and Kidane [the inventors on the Patents-in-Suit] did the formulation work." Defendants' Responsive Post-Trial Brief ("Defs. Resp. Br.") at 18 [Docket No. 404]. As such, this is not particularly probative of failure of others. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 759 (N.D. W.Va. 2004) aff'd, 161 F. App'x 944 (Fed. Cir. 2005).

It is clear, though, that Actavis also attempted to develop many different extended release formulations of oxcarbazepine before arriving at the present accused tablets over the course of several years. See, e.g., Tr. 1641:18-1642:7, 1643:14-1651:8

(Little Direct); PTX 72.12-14, 26-28; PTX 74.27-28; PTX 76.27-28. Certain of these formulations, for example, included the element 1(d) release promoting agent only in the coating of the tablet. Tr. 1645:16-1648:21 (Little Direct); PTX 72.26-28; PTX 76.27-28. These formulations, however, were deemed as failures as they did not pass bioequivalence testing. Tr. 1641:18-1651:8 (Little Direct); PTX 351.1.[25]

The Court finds that the record indicates that others had previously failed to develop an effective once daily oxcarbazepine formulation and, as such, supports a finding of non-obviousness.

(4) Surprising and Unexpected Results

"[U]nexpected results can, in appropriate circumstances, be sufficient standing alone to preclude a finding of obviousness." Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186, 1200 (Fed. Cir. 2014). The Plaintiff relies nearly exclusively upon the testimony of Dr. Wheless regarding surprising and unexpected results.

[25] Supernus also urges the Court to consider evidence of copying as an indicia of non-obviousness. As the Defendants and the Federal Circuit repeatedly point out, however, "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013) (citing Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 377 F. App'x 978, 983 (Fed. Cir. 2010)).

Based upon his own experience as a neurologist and epileptologist, Dr. Wheless testified that Oxtellar XR® exhibits surprising and unexpected results. Tr. 1207:14-23 (Wheless Direct). His patients have reported "that they were dramatically better on [Oxtellar XR®] from both a side effects standpoint and efficacy standpoint." Id. at 1207:16-18. Dr. Wheless has heard similar accounts from other physicians across the country. Id. at 1207:19-23, 1208:5-9. Dr. Wheless also testified regarding testimonials received by Supernus from patients and physicians that documented patients achieving seizure freedom on Oxtellar XR® despite having long-standing epilepsy and not having achieved seizure freedom on other anti-epileptic drugs. Id. at 1208:10-23.

Actavis challenges Supernus by arguing that the benefits of Oxtellar XR®, to the extent they exist, are not surprising or unexpected. See Defs. Br. at 28-29. Dr. Wheless testified that prior to Supernus's invention, immediate release oxcarbazepine was known to have "fewer drug interactions because it was metabolized differently in the body and it also had fewer side effects," when compared to carbamazepine. Tr. 1190:13-17 (Wheless Direct). The fact that extended release oxcarbazepine would exhibit similar properties is neither surprising nor unexpected.

The record additionally supports Actavis's position that it was known that extended release formulations of any drug generally have a lower incidence of side effects compared with an immediate release formulation of the same drug. Dr. Wheless explained that, after the release of immediate release oxcarbazepine, the "next obvious kind of thought" was to develop an extended release oxcarbazepine as that "should improve the side effects, even more the tolerable [sic], allow us to use this molecule better, if you will, and it will also improve adherence." Id. at 1190:18-24. Dr. Hopfenberg also testified that it was known that controlled or extended release formulations, generally speaking, have better side effect profiles than immediate release drugs. Tr. 1437:13-1438:20 (Hopfenberg Direct). Dr. Fred Lado, Actavis's expert neurologist, also testified that fewer side effects are "exactly why we formulate medications into an extended release" in the first place and, therefore, "that's entirely the expected result." Tr. 1257:15-1258:4 (Lado Direct).

The Court is not persuaded that Oxtellar XR® exhibited surprising and unexpected results and this factor does not support a finding of non-obviousness.

(5) Industry Praise

"Praise and industry acceptance provide additional evidence of nonobviousness." Janssen Products, L.P. v. Lupin Ltd., 109

F. Supp. 3d 650, 671 (D.N.J. 2014) (citing Power-One, Inc. v. Artesyn Techs., Inc., 599 F.3d 1343, 1352 (Fed. Cir. 2010) and Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1574 (Fed. Cir. 1996). Supernus relies upon the testimony of Dr. Wheless and a survey of physicians who prescribed Oxtellar XR® to establish industry praise and acceptance.

Dr. Wheless testified that, based upon his experience as a neurologist treating patients with epilepsy and testimonials received by Supernus, he believes Oxtellar XR® has received industry praise and professional approval. Tr. 1210:6-1211:14 (Wheless Direct). He additionally relied upon a survey of physicians who have prescribed Oxtellar XR®, conducted by Supernus, to come to this conclusion. Id. at 1210:9-10; PTX 409.24-25.

According to this survey, 35% of doctors who had previously prescribed Oxtellar XR® were "somewhat likely" to recommend it to their colleagues, whereas 46% were "very likely" and 13% were "extremely likely" to recommend it. PTX 409.24. None of these doctors reported that they would not recommend Oxtellar XR® to their colleagues and 6% reported they were "not too likely" to recommend it. Id. Of the 71 physicians in the survey who had prescribed Oxtellar XR®, 42% reported that a major factor in their decision to prescribe Oxtellar XR® was that it was a

"significant improvement over immediate-release" oxcarbazepine. PTX 409.25. This was a minor factor for an additional 52%. Id.

The results of the survey indicate at least some praise and acceptance in the industry. The Court, however, affords little weight to the survey since there is no evidence in the record that it has been validated.[26] Additionally, the survey only polled 150 physicians who had received at least one sales call from Supernus. What's more, the figures outlined above only include the responses of the 71 physicians who reported having prescribed Oxtellar. It is not clear to the Court whether this is a sufficient sample size from which to draw any meaningful conclusions. Even if the Court were to credit the survey, it makes clear that only 47% of the 150 physicians who received Oxtellar XR® sales calls actually prescribed the drug. PTX 409.16. Supernus's own records indicate that only 21% of physicians who received Oxtellar XR® sales calls went on to prescribe Oxtellar XR®. PTX 409.20. This is not suggestive of industry praise and acceptance.

[26] Supernus argues that its survey is reliable as it was "conducted by a global market research firm outside the context of this case." Pl. Resp. Br. at 22. This alone is not evidence of its validity. Regardless, the survey remains one commissioned by Supernus for use in its board presentation and the Court does not find it to be particularly persuasive evidence of industry praise and acceptance. See Bayer Healthcare Pharms., Inc. v. Watson, Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("self-referential commendation fall[s] well short of demonstrating true industry praise.").

While the Court found Dr. Wheless to be quite credible and persuasive, his praise and acceptance of Oxtellar XR® is insufficient to carry this factor for Supernus. Accordingly, the Court finds that Supernus has not sufficiently established this indicia of non-obviousness.

(6) Commercial Success

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." Merck & Co., Inc. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005). Evidence of commercial success is probative of non-obviousness where there is "some causal relation or 'nexus'" between the invention and the commercial success of the invention's commercial embodiment. Id. Supernus relied largely on the testimony of Victor Vaughn, its VP of Sales and Marketing, and Dr. Gordon Rausser, its expert economist, to establish this factor.

The evidence shows that the number of Oxtellar XR® prescriptions is growing over time, Tr. 176:15-177:9 (Vaughn Direct), and that, on a launch-aligned basis, Oxtellar XR® "performed as well if not better than" most other AEDs. Id. at 178:1-6. The net product sales of Oxtellar XR® for the fourth quarter of 2014 were approximately $7.6 million, according to Mr. Vaughn. For that same period, the estimated profitability

of Oxtellar XR® was around $1.2 million. Id. at 191:12-17. Mr. Vaughn testified that Oxtellar XR® was "clearly profitable for the year, first full year of launch for 2014." Id. at 187:14-18.

Dr. David Blackburn, Actavis's expert economist, however, interpreted Oxtellar XR®'s sales figures differently. He testified that Oxtellar XR®'s sales levels "[a]re relatively low. They're low for a pharmaceutical product. The level of prescriptions are low. And on top of being at a low level, they are not growing at a rate that would cause anyone to project substantial sales in the future." Tr. 1743:9-16 (Blackburn Direct). Additionally, the approximately 7,000 prescriptions per month that Oxtellar XR® has earned in the two years since its launch "is not a substantial level of prescriptions" compared to other AEDs on the market, in Dr. Blackburn's opinion. Id. at 1744:25-1745:5; DTX 201 at SUP-OXT00817437. Dr. Blackburn concluded that Oxtellar XR®'s "level of sales is not something that stands out in the AED space. . . . it's not a number indicative of success." Tr. 1746:17-21 (Blackburn Direct).

There is also a dispute as to Oxtellar XR®'s market share. Dr. Rausser testified that Oxtellar XR® was commercially successful as, within two years, it "was able to capture 34 percent of the total branded molecule [oxcarbazepine] for which there were prescriptions written. . . . In other words, it is

capturing a material proportion of what is available to Oxtellar XR® on the market." Tr. 1538:19-25 (Rausser Direct).

Actavis, however, challenges the credibility of Dr. Rausser's analysis. In Actavis's view, Dr. Rausser's analysis is based on the fundamentally flawed premise that the relevant market for Oxtellar XR® is branded oxcarbazepine alone, as opposed to all prescriptions for oxcarbazepine. Defs. Br. at 30. This ignores the generic oxcarbazepine drugs which make up the vast majority of oxcarbazepine prescriptions. Defs. Resp. Br. at 20. The Court is persuaded by Actavis's position. Even Supernus's internal documents describe Oxtellar XR®'s market share after two years as 2.3% of the relevant market, suggesting that Supernus views the relevant market to include all oxcarbazepine prescriptions. See DTX 201 at SUP-OXT00817432. Mr. Vaughn likewise testified that Supernus's objective was to "convert oxcarbazepine to Oxtellar XR®." Tr. 255:9-13 (Vaughn Cross). Mr. Vaughn does not limit the objective to conversion of only branded oxcarbazepine prescriptions, namely those for Trileptal®, to Oxtellar XR®, as that would exclude the vast majority of oxcarbazepine prescriptions.

The Court views this evidence in the context of the AED market. Dr. Rausser explained that there are economic barriers to entering the AED market given doctors' reluctance to changing a patient's medication unless their seizures are poorly

controlled. Tr. 1514:1-6, 1517:19-1519:1; 1539:11-12 (Rausser Direct). Doctors are even reluctant to change a patient to a different version of the same molecule, for example from immediate release oxcarbazepine to extended release oxcarbazepine. Id. at 1518:19-22. Indeed, Dr. Lado, Actavis's expert neurologist, confirmed that "patients and doctors tend to be fairly conservative in changing medications when they have seizure control." Tr. 1257:4-5 (Lado Direct); see also Tr. 170:9-15 (Vaughn Direct) ("Keep in mind epilepsy is a very serious disorder. When a patient has a breakthrough seizure it has devastating effects on that patient, as well as the family. . . . so for that reason physicians are very hesitant to switch a patient from one products [sic] to another.").

In sum, the evidence demonstrates that Oxtellar XR® has been neither a "blockbuster success," as Supernus contends, nor a "lackluster product," as Actavis intimates. It has captured only a small portion of the oxcarbazepine market thus far. However, it has performed adequately compared to its competitors, especially in light of the barriers to entry in the AED market; moreover, it has achieved some degree of profitability in its roughly two years on the market. Ultimately, the Court finds that this factor is neutral.

d) Conclusions of Law

After carefully considering the Graham factors, the Court concludes that Claim 1 of the Patents-in-Suit is valid and would not have been obvious to a person of ordinary skill in the art in 2007. The prior art did not disclose all of the elements of the invention and the Defendants have not provided the Court with sufficient evidence to establish that a person of ordinary skill in the art would have had a motivation to combine the prior art references with a reasonable expectation of success. Therefore, Actavis has failed to rebut the presumption of validity by establishing by clear and convincing evidence that the Patents-in-Suit are invalid as obvious.[27]

The dependent claims likewise are valid, as they depend upon an independent claim that is valid. Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd., 2011 WL 4527353, at *5 (W.D. Pa. Sept. 28, 2011) (citing Wahpeton Canvas Co., Inc. v. Frontier, Inc., 870 F.2d 1546, 1552 n. 9 (Fed. Cir. 1989)) ("Therefore, if a dependent claim depends upon an independent claim that is held valid, the dependent claim must also be valid as at least one of its elements necessarily is not anticipated by the prior art.").

[27] Nonetheless, the Court has evaluated the secondary considerations. As a whole, the Court considers the secondary considerations to be neutral on the record before it.

2. Written Description

Actavis contends that the Patents-in-Suit are invalid for lack of a written description of a homogeneous matrix. Actavis also argues that the '600 Patent is invalid for lack of a written description of the *in vitro* dissolution limitations in Claim 1.

In pertinent part, 35 U.S.C. § 112 provides:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Pursuant to 35 U.S.C. § 112, a patentee must provide a written description that allows a person of ordinary skill in the art to recognize that the patentee invented what is claimed. "The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the [invention] as described in the patent specification." Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345 (Fed. Cir. 2010).

In order to satisfy the written description test, the application must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad Pharms., Inc. v. Eli Lilly

& Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010); Centocor Ortho Biotech, Inc. v. Abbott Labs, 636 F.3d 1341, 1348 (Fed. Cir. 2011). The "level of detail required . . . varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." Ariad Pharms., 598 F.3d at 1351.

Actavis makes two arguments as to its written description defense. First, it argues that the "homogeneous matrix" limitation was not described in the Patents-in-Suit. Specifically, Actavis argues, the specification describes just the structure formed by the matrix polymer when it is fully hydrated and in a state of equilibrium and does not include the other ingredients – the drug, solubility enhancer, and pH-dependent polymer – of the formulation, the focus being the state of the medication during its intended use. Actavis argues that this description is different from the way it was used in the claims. Further, Actavis characterizes the working example recited in the specification as a "superficial" one and contends that a person skilled in the art would not conclude that a tablet in which all ingredients were uniformly dispersed was made. Defs. Br. at 32-33. The Court disagrees.

The specification and prosecution history convey to persons of ordinary skill in the art that, as of the filing dates, Supernus was in possession of the claimed invention. Example 4

explicitly (not superficially) discloses the step by step manufacturing process used by the inventors to produce a homogeneous matrix tablet. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-66 (Fed. Cir. 1991) (drawing must convey with reasonable clarity that applicant was in possession of the later-claimed invention including all the limitations and elements). Indeed, as the prosecution history demonstrates, the inventors amended Claim 1 to recite a homogeneous matrix derived according to the protocols set forth in the examples of the Patents-in-Suit. PTX 5.298; Tr. 613:12-614:22 (Little Direct). In the high shear granulation manufacturing process disclosed in Example 4, all of the ingredients except for magnesium stearate – oxcarbazepine, Prosolv SMC C50, PVP K25, HPMC K4M, and Eudragit L100-55 - are mixed together. See '898 Patent, col. 4, ll. 40-42; see also Tr. 464:16-22 (Kidane Depo).

Indeed, Actavis's expert, Dr. Hopfenberg, agreed on cross-examination that a person of skill in the art making a matrix tablet would be able to create a homogeneous matrix formulation:

> Q. Would you agree that absent a specific objective not to be homogeneous, the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation that would comprise a uniform dispersion of ingredients?
>
> A. I think that would be an obvious objective of the skilled formulator.
>
> Q. So you would agree with that statement?

> A. I would.
>
> Q. You would also agree that the objective of the person of ordinary skill in the art forming such a matrix device would be to form a homogeneous matrix in the absence of any disclaimer to the contrary. Do you agree with that statement?
>
> A. I believe I would give the same answer I did before, the person of ordinary skill in the art formulating a matrix-based formulation -- the person of ordinary skill in the art developing a matrix-based formulation would have as an objective the formation of a homogeneous matrix.
>
> Q. And you would agree, finally, Dr. Hopfenberg, that there can still be a resulting homogeneous matrix if some ingredients are added before granulation and some ingredients are added after granulation, correct?
>
> A. I think anything is possible, but the -- that's possible.

Tr. 1493:12-1494:9 (Hopfenberg Cross).

Actavis argues that Supernus's reliance upon Dr. Hopfenberg's testimony is misplaced because Dr. Hopfenberg simply described in general terms what a person skilled in the art would like to achieve in a formulation, that is, a homogeneous matrix, and not the invention. This Court disagrees. The specification sets forth the manufacturing process in Example 4 how to produce a homogeneous matrix. When the term "homogeneous matrix" was added to the claim to address the Examiner's concerns, the applicants stated that "one of ordinary skill in the art would appreciate that the formulations derived according to the protocol set forth in the Examples

would necessarily comprise a homogeneous matrix." PTX 5.298. This is the "descriptive matter" that goes beyond simply describing the prior art as Actavis argues. Cf. Tronzo v. Biomet, Inc., 156 F.3d 1154, 1159 (Fed. Cir. 1998) (simply describing prior art does not meet the written description requirement).

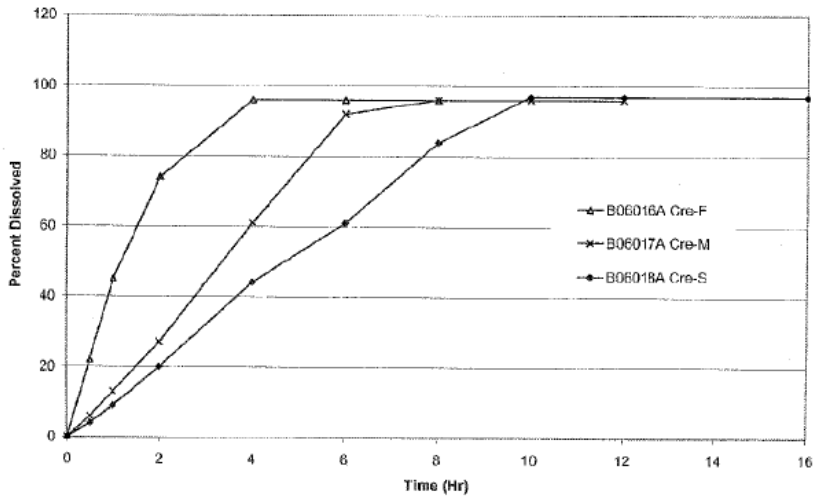
The Court now turns to Actavis's argument regarding the '600 Patent, even though it has found no infringement. Claim 1 of the '600 Patent includes the *in vitro* dissolution limitations to the formulation claimed:

> wherein, in vitro:
>
> (i) between 20 and 74% of the total oxcarbazepine is released by 2 hours; and
>
> (ii) between 44 and 96% of the total oxcarbazepine is released by 4 hours.

Actavis acknowledges that the range numbers were selected from Figure 6, with the lower numbers from the bottom curve and the higher numbers from the top curve. DFOF ¶¶ 525-530. The Defendants argue, however, that Supernus impermissively claimed an expansive range by "mixing and matching arbitrary points on dissolution curves of different formulations." Defs. Br. at 33-34; see also DFOF ¶¶ 523-29. Thus, Dr. Hopfenberg testified, a person skilled in the art would not consider the inventors to be in possession of such breadth. Tr. 1399:9-13 (Hopfenberg Direct). The Court disagrees.

The standard for written description does not require an inventor "to reduce to practice and be in physical possession of every species." Pfizer Inc. v. Teva Pharm. USA, Inc., 555 F. App'x 961, 968 (Fed. Cir. 2014). Figure 6 of the Supernus Patents illustrates three exemplary dissolution profiles for the fast (CRe-F), medium (CRe-M), and slow (CRe-S) oxcarbazepine formulations.

FIGURE 6



The '600 Patent states that USP Apparatus II at 60 RPM was used, and the dissolution medium was 1% SLS in water. '600 Patent, col. 3, ll. 24-25. This is sufficient to allow a person skilled in the art to know that the inventors were in possession of at least three formulations with *in vitro* release profiles covered by Claim 1.

3. Indefiniteness

Finally, Actavis argues that the Patents-in-Suit are invalid as indefinite because the specification and prosecution history contain no guidance on how to determine if a matrix is homogeneous. Actavis further argues that the *in vitro* limitations in the '600 Patent are indefinite because they provide no guidance on what set of conditions do or do not control in producing the claimed ranges.

Pursuant to 35 U.S.C. § 112(b), "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention." The Supreme Court has explained that this requirement "entails a 'delicate balance.'" Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2128 (2014) (quoting Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 731 (2002)). Section 112(b) requires that a patent "be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." Id. at 2129 (internal citations and quotations omitted). Nonetheless, it also recognizes "the inherent limitations of language" and permits "[s]ome modicum of uncertainty." Id. at 2128.

In other words, Section 112(b) requires that "a patent's claims, viewed in light of the specification and prosecution

history, inform those skilled in the art about the scope of the invention with reasonable certainty." Id. at 2129. "The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable." Id.

As for the term "homogeneous matrix," Actavis contends that there is nothing in the specification that sets a "clear line" between a matrix that is homogeneous and one that is not. Defs. Br. at 37. To prove its point, Actavis remonstrates that even Dr. Bugay testified that there was no generally recognized standard, including the standard technique of chemical imaging, that could answer the question of whether a distribution of ingredients was uniform or not. Id. Actavis's protestations are actually borne out of its undue emphasis on chemical imaging and eschewal of the understanding of a homogeneous matrix by a person of ordinary skill in the art.

It is clear that persons skilled in the art understood that "homogeneous" means a mixture of two or more ingredients that are uniformly dispersed in a pharmaceutical formulation. Throughout the trial, it was evident that persons skilled in the art understood that homogeneity varied in degrees. As set forth above, both parties' experts agreed. See Tr. 904:8-12 (Muzzio Direct); Tr. 377:1-19 (Bugay Cross). Moreover, persons skilled in the art also understood that perfect homogeneity was not achievable because perfect molecular uniformity in a

pharmaceutical formulation was not possible. Tr. 341:20-23 (Bugay Direct); Tr. 373:3-22 (Bugay Cross). Additionally, as Dr. Little persuasively testified, a person skilled in the art could turn to FDA uniformity testing to confirm that a particular manufacturing process worked as intended. See Tr. 634:14-635:3 (Little Direct). Indeed, Example 4 discloses the manufacturing step by step process the inventors used to produce a homogeneous matrix tablet. As this Court has stated, supra at footnote 14, chemical imaging is a standard that confirms homogeneity, but it is not essential to the Patents-in-Suit to survive an indefiniteness challenge.

As to Claim 1 of the ’600 Patent, although the Court need not reach this issue, the Patent is not indefinite. The ’600 Patent discloses a standard set of dissolution test conditions, to wit, USP Apparatus II, 60 RPM, 1% SLS, that could be implemented by a pharmaceutical formulator.

Accordingly, the Patents-in-Suit are not invalid as indefinite.

IV. CONCLUSION

For the foregoing reasons, the Court finds that the Defendants’ ANDA product will infringe the ’898 Patent and the ’131 Patent. The Court, however, finds that the Defendants’ ANDA product will not infringe the ’600 Patent. The Court additionally finds that all three Patents-in-Suit are valid.

Accordingly, the Court enters judgment in favor of Supernus and against Actavis as to the ’898 Patent and the ’131 Patent, and in favor of Actavis and against Supernus as to the ’600 Patent. Actavis’s oral motion for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) is GRANTED as to the ’600 Patent. An appropriate Order will issue herewith.

s/Renée Marie Bumb
RENÉE MARIE BUMB
UNITED STATES DISTRICT JUDGE

Dated: February 5, 2016